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POLYNEURITIS

A CLINICAL AND PATHOLOGIC STUDY OF A SPECIAL GROUP OF CASES FREQUENTLY REFERRED TO AS INSTANCES OF NEURONITIS

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This study was prompted by the definite increase in the number of cases of polyneuritis which we have observed in the past three years. We are cognizant of the confusion that exists in the literature regarding the terminology of polyneuritis and shall avoid entering into a discussion of the merits of the numerous terms which are employed to describe what appear to be minor variations of the same disease process. We propose to consider in this study a series of cases which have been encountered at the Mayo Clinic in the last fifteen years. These, we believe, can be classified under one heading and should be isolated from the large group of cases of polyneuritis in which the condition is due to various and sundry causes. We have adopted the term "neuronitis" to designate the disease in this series of cases. While certain peculiarities, such as facial diplegia and choked disks, were present in some of the cases, it seems proper to collect them under this special heading.

The disease in the majority of cases in our series is preceded by a mild transitory infection. Following recovery from this there is a latent period of from a few days to several months, during which there is complete freedom from symptoms. Then, rather suddenly, weakness or paresthesia of the extremities sets in; this is often more marked in the legs than in the arms. Sensory symptoms are not marked,

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although they are usually present to some degree. Sphincteric control may or may not be disturbed; usually it is not. Frequently the facial muscles are affected, whereas other evidences of involvement of cranial nerves are infrequent. Pain is not a prominent part of the picture, although it may be present to a marked degree. The course of the disease is usually afebrile; the condition may be fatal, but usually the outcome is favorable, with complete recovery in from six months to two years. An almost invariable accompaniment is a high total value for protein in the cerebrospinal fluid associated with little or no increase in the cell count. Pathologically, the peripheral nerves show degeneration of myelin and fragmentation of the axis-cylinders without any evidence of inflammation. The dorsal root ganglia show lymphocytic infiltration, while the remainder of the nervous system appears essentially normal.

A comprehensive review of the literature covering the subject is beyond the scope of this paper. Cobb and Coggeshall [1] have recently reviewed the entire problem of neuritis, and from this study it is evident that much added work is necessary for a thorough understanding of this syndrome. It is hoped that our contribution may aid in establishing a clearer understanding of one group of cases of multiple neuritis and not add more confusion to an already overburdened literature.

As the term neuronitis is used by us as a subheading, we were interested in determining who originally employed it. To the best of our knowledge the first mention of neuronitis was made by Mills [2] in 1898. In the course of a discussion advocating reclassification of nervous diseases in the light of the then new neuron theory, he suggested the diagnosis neuronitis, while at the same time acknowledging that the term had an "unnatural sound even to a neurologic ear." Foster Kennedy,[3] in 1919, again made use of the term and undoubtedly had in mind a disease entity that he wished to distinguish from the disorder in the general group of cases of polyneuritis. Other writers in describing the same condition or variations of it have used such terms as polyneuronitis, radiculoneuritis, myeloradiculitis, and so forth, making it practically impossible to obtain a clear understanding of the problem. Osler [4] in 1892 described a syndrome which closly resembles the one

1. Cobb, Stanley, and Coggeshall, H. C.: Neuritis, J. A. M. A. **103**:1608 (Nov. 24) 1934.

2. Mills, C. K.: The Reclassification of Some Organic Nervous Diseases on the Basis of the Neurons, J. A. M. A. **31**:11 (July 2) 1898.

3. Kennedy, Foster: Infective Neuronitis, Arch. Neurol. & Psychiat. **2**:621 (Dec.) 1919.

4. Osler, William: Principles and Practice of Medicine, ed. 1, New York, D. Appleton and Company, 1892; ed. 8, New York, D. Appleton and Company, 1916, p. 1022.

we are presenting and named it acute febrile polyneuritis. Patrick [5] in 1916 emphasized the occurrence of facial diplegia in the syndrome of polyneuritis. Gordon Holmes [6] in 1917 described a group of cases which he observed while in the army and designated the condition as acute febrile polyneuritis. His patients gave no evidence of changes in the cerebrospinal fluid. Bradford, Bashford and Wilson [7] in 1918 described a series of cases under the classification acute infective polyneuritis. In their cases the spinal fluid was normal. In most of their cases the disease was accompanied by involvement of the facial nerve. The mortality was 26.6 per cent. At necropsy they found degeneration of the peripheral nerve fibers and also changes in the spinal cord. Casamajor [8] in 1919 mentioned a condition which may be similar and called it acute ascending paralysis. In 1927 Viets [9] described two cases under the heading acute polyneuritis with facial diplegia. He mentioned the high total protein content of the spinal fluid and the relatively low cell count. Strauss and Rabiner [10] in 1930 suggested the term myeloradiculitis for a syndrome which appeared to belong in the same category. Cobb and Coggeshall's case 1, an instance of "acute infectious febrile polyneuritis," certainly appears to belong in this group.

In the past few years a condition has been observed in pregnant women which has been described by many authors, including among others Strauss and McDonald,[11] Lubin,[12] Maisel and Woltman [13] and Berkwitz and Lufkin.[14] Almost without exception these authors have used the term neuronitis to describe the condition. It remains a debatable question whether all these cases represent instances of a deficiency disease and require a special grouping.

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5. Patrick, H. T.: Facial Diplegia in Multiple Neuritis, J. Nerv. & Ment. Dis. **44**:322 (Oct.) 1916.

6. Holmes, Gordon: Acute Febrile Polyneuritis, Brit. M. J. **2**:37 (July 14) 1917.

7. Bradford, J. R.; Bashford, E. F., and Wilson, J. A.: Acute Infective Polyneuritis, Quart. J. Med. **12**:88 (Oct.) 1918.

8. Casamajor, Louis: Acute Ascending Paralysis Among Troops: Pathologic Findings, Arch. Neurol. & Psychiat. **2**:605 (Dec.) 1919.

9. Viets, H. R.: Acute Polyneuritis with Facial Diplegia, Arch. Neurol. & Psychiat. **17**:794 (June) 1927.

10. Strauss, Israel, and Rabiner, A. M.: Myeloradiculitis: A Clinical Syndrome with Report of Seven Cases, Arch. Neurol. & Psychiat. **23**:240 (Feb.) 1930.

11. Strauss, M. B., and McDonald, W. J.: Polyneuritis of Pregnancy: A Dietary Deficiency Disorder, J. A. M. A. **100**:1320 (April 29) 1933.

12. Lubin, Samuel: Toxic Neuronitis of Pregnancy, Am. J. Obst. & Gynec. **26**:442 (Sept.) 1933.

13. Maisel, J. J., and Woltman, H. W.: Neuronitis of Pregnancy Without Vomiting, J. A. M. A. **103**:1930 (Dec. 22) 1934.

14. Berkwitz, N. J., and Lufkin, N. H.: Toxic Neuronitis of Pregnancy: A Clinicopathological Report, Surg., Gynec. & Obst. **54**:743 (May) 1932.

A condition which at first glance seems to be indistinguishable from that in our series of cases likewise has been called by different names. We refer to cases in which symptoms referable to the cord are present in conjunction with edema of the optic disks. The condition in such cases has been variously termed neuromyelitis optica, optic neuromyelitis, and so forth. Necropsy in these cases reveals what seems to be a multiple sclerotic or encephalomyelitic type of pathologic change, and this condition is not to be confused with neuronitis unless this specific infection may at times affect the peripheral neuron and at other times affect both the peripheral nerves and the central nervous system. Mention is made of this because in our group we have included three cases of polyneuritis or neuronitis accompanied by edema of the optic disks. Taylor and McDonald [15] reported several cases of polyneuritis with facial diplegia in which papilledema was present.

OBSERVATIONS

Since 1918, we have observed thirty-five cases of polyneuritis which we believe belong in a specific series, and for the condition present in these cases we have adopted the previously employed term neuronitis. Of these thirty-five cases, fifteen must be removed from present consideration because of lack of complete examination of the spinal fluid. Most of the patients in these fifteen cases were seen before 1927, at which time routine determinations of the total protein content in the spinal fluid were not made. Among these fifteen there were also cases in which we did not observe the patient until late in the course of the disease and in which examination of the spinal fluid was not made. Observations on the remaining twenty cases are given in the table.

The incidence in the two sexes in our series was about equal, 40 per cent of the patients being males and 60 per cent females. The ages varied from 2½ to 52 years, the majority of the patients being in the third decade of life. Approximately half of the patients (60 per cent) had a previous infection, usually influenza or another infection of the upper portion of the respiratory tract. This acute infection was followed by a latent period of apparent well-being, which varied from a few days to several months, the average duration being seven weeks. That all the patients did not give a history of a preceding infection does not exclude the possibility of an infection having occurred.

The most common original complaint was paresthesia of the extremities, which occurred in 55 per cent of the cases. The next most frequent complaint was moderate pain and discomfort in the limbs; it was present in 40 per cent of the cases. Other initial symptoms, in

15. Taylor, E. W., and McDonald, C. A.: A Syndrome of Polyneuritis with Facial Diplegia, Arch. Neurol. & Psychiat. **27**:79 (Jan.) 1932.

the order of frequency, included weakness of the legs, weakness of the arms and facial weakness. In all instances there was a tendency to steady progression. If the condition began in the legs, extension was usually upward; if it began in the arms or face it later passed to the legs. Invariably the distal portions of the limbs were most severely affected.

In all instances motor involvement was the outstanding finding. In some cases it was so profound that the patient became entirely helpless, and if he also had facial diplegia he presented a pathetic picture. There was never any appreciable atrophy beyond what might be the result of disuse. Fibrillary twitchings were not observed. As might be anticipated, the deep reflexes were diminished or absent.

Subjective sensory complaints were always present, but in only two thirds of the cases could objective sensory changes be demonstrated. Joint sense and vibration sense were diminished more markedly than the sense of pain, touch and temperature. At no time did the sensory changes appear as profound as the motor changes. In most instances the patients complained of muscular pain and tenderness, but in only one case was pain of marked severity.

In 35 per cent of the cases facial weakness occurred; hence the name polyneuritis and facial diplegia. Three of our patients had choked disks, and two of these made a complete recovery; the other died, but a postmortem examination was not made.

One of the most constant and characteristic findings in this series of cases was the presence of changes in the spinal fluid. There was a distinct dissociation between the total protein content and the cell count. This was true in all the twenty cases. The total protein content varied from 100 to 800 mg. for each 100 cc. of spinal fluid. It was noted that in the early period of progression the total protein content in the cerebrospinal fluid steadily increased (case 2). The number of cells in the cerebrospinal fluid varied between 1 and 80 cells per cubic millimeter, the average number being 12 cells, which were mainly lymphocytes. In all but three cases the cell count was less than 24. As did the total protein content, the number of cells had a tendency to increase with the acute progress of the disease. The colloidal gold curves were of midzone character in 50 per cent and of first zone type in 25 per cent of the cases. In five cases no study of the colloidal gold curve was reported. In four cases the spinal fluid had a xanthochromic color. Needless to say, the result of the flocculation test for syphilis was negative in all cases.

As stated, the course of the disease was usually afebrile. In a few instances during the first week of the illness there was slight fever, the temperature not exceeding 100 F. In one case there was a terminal

Data on Twenty Cases of Neuronitis

Case	Age, Yrs.	Sex	Previous Illnesses	First Symptom, Date	Motor Disturbances	Sensory Disturbances	Reflexes*	Examination of Spinal Fluid: Nonne Reaction	Lymphocytes†	Neutrophils†	Total Protein‡	Color	Colloidal Gold Curve (Zone)	Remarks
1	44	M	None	Pain in legs, August 1928	Bilateral facial weakness; arms weak; legs very weak	Paresthesia in arms and legs	Arms, —1; legs, —4	+	70	6	400	Clear	Mid.	Facial palsy; death, Feb. 27, 1929
2	43	F	None	Difficulty in walking, December 1929	Arms and legs weak	Mild changes, especially in joint and vibration sense	Arms, —1; legs, —4	+	3	..	80	Clear	First	Some residual weakness, August 1931
3	22	F	Cold, Dec. 1, 1930	Numbness of toes, Dec. 31, 1930	Arms and legs very weak	Mild changes; joint and vibration sense most affected	Arms, —3 to —4; legs, —4	+	2	..	800	Yellow	Mid.	Diplopia; urinary incontinence; outcome unknown
4	23	M	None	Numbness in legs, September 1931	Left facial weakness; arms and legs weak	Paresthesia	Arms, —1 to —2; legs, —4	+	3	..	160	Yellow	Mid.	Facial palsy; outcome unknown
5	39	F	Previous infection(?)	Pain and numbness in feet, January 1931	Arms and legs weak, especially legs	Mild changes, especially in joint and vibration sense	Arms, —2 to —3; legs, —4	+	9	..	400	Yellow	First	Long course, well after 2½ years
6	36	F	"Flu," June 1932	Weakness of legs, May 1932	Marked weakness of legs	No objective changes	Arms, —1 to —2; legs, —4	+	2	..	200	Clear	First	Practically well by August 1932
7	43	M	None	Numbness of hands, January 1932	Bilateral facial weakness; arms weak	Mild changes in arms	Arms normal; knees normal; ankle, —3	+	80	..	100	Clear	First	Facial palsy; recovery in 5 months
8	37	F	Grip, February 1932	Numbness in legs, July 1932	Arms and legs weak, especially legs	Mild changes; joint and vibration sense most affected	Arms, —4; legs, —4	+	3	..	400	Clear	Mid.	Choked disks, —2 to —3 diopters; death, July 15, 1933; cause undetermined
9	2½	F	Cold, December 1933	Weakness in legs, December 1933	Arms and legs very weak	No objective changes	Arms, —4	+	1	..	2+	Clear	.....	Gradual improvement

10	14	M	Grip, October 1933	Legs weak one week later	Arms and legs weak	Mild changes in legs	Arms, —4; legs, —4	+	3	..	140	Clear	Mid.	Complete recovery by December 1934
11	29	F	Cold, July 3, 1933	Weakness in legs, July 12, 1933	Legs very weak; arms slightly affected	Mild changes; joint and vibration sense markedly affected	Arms, —3; legs, —4	+	4	..	400	Clear	Mid.	Complete recovery by end of eighth month
12	46	M	None	Numbness in legs, November 1933	Legs weak	Joint and vibration sense impaired in legs	Arms normal, legs, —3 to —4	+	3	..	160	Clear	Mid.	Weakness still present at end of one year
13	6	F	Scarlet fever, February 1934	Weakness in legs, April 1934	Arms and legs very weak	No objective changes	Arms, —3; legs, —4	+	1	..	200	Clear	.....	Complete recovery in eight months
14	25	F	Not definite	Headaches and numbness in limbs, February 1934	Facial weakness; arms and legs very weak	Mild changes, especially in joint and vibration sense	Arms, —3; legs, —4	+	13	11	400	Clear	Mid.	Choked disks; complete recovery in nine months
15	45	M	"Flu," February 1934	Facial weakness one week later	Facial weakness; arms and legs slightly weak	Mild changes	Arms, —4; legs, —4	+	1	..	200	Clear	Mid.	Facial weakness; recovery in three months
16	4	M	Sore throat, February 1934	Weakness in legs, July 1, 1934	Facial weakness; arms and legs weak	No change	Arms, —3; legs, —4	+	8	..	240	Clear	.....	Facial weakness; recovery in five months
17	12	F	Fever, September 1934	Pain in legs one week later	Legs slightly affected	No change	Arms, —2; legs, —3 to —4	+	5	..	120	Clear	.....	Weakness still present in legs October 1934
18	52	M	Grip, November 1934	Herpes, December 1934; facial weakness	Bilateral facial weakness; limbs weak	Change in right side of face, hands and legs	Arms, —3 to —4; legs, —3 to —4	+	2	..	180 500	Yellow	.....	Facial weakness; death, Feb. 11, 1935
19	39	F	Cold, December 1934	Weakness in legs, January 1935	Marked weakness of arms and legs	Slight changes; joint and vibration sense most affected	Arms, —3; legs, —4	+	1	..	160	Clear	Mid.	Patient alive but very weak, April 1935
20	27	M	None	Weakness in legs, October 1934	Arms and legs weak	Slight changes; joint and vibration sense most affected	Arms, —2; legs, —4	+	16	..	100	Clear	Mid.	Death, March, 1935, Hodgkin's disease

* The figures —1 to —4 express the degree of impairment.
† The number of cells is given per cubic millimeter of fluid.
‡ Mg. per hundred cubic centimeters.

high fever. The entire duration of the illness, from the time of onset of paresthesia or weakness until complete recovery, varied from ten weeks to two and a half years, the average duration being six and six-tenths months. The acute stage of the illness usually lasted two or three months, the remaining time being consumed in the process of recovery. There were four deaths in the series of twenty cases, or a mortality rate of 20 per cent. The mortality rate for the thirty-five cases was 14 per cent. As far as we know all the patients who have recovered from the acute disease have made a practically complete recovery and have had no recurrence of the symptoms. We have seen some faulty regeneration or slight residual weakness but never any gross defect.

It is interesting to note that in the past three years there seems to have been an increase in the incidence of the disease. Eight of our cases were observed in 1934 and four in 1933; the remaining eight were distributed over the preceding four years. Thus far in 1935 (April 1), we have had three cases. It appears from our study that the condition is distinctly on the increase.

REPORT OF CASES

It is unnecessary to report all the cases in detail. The following four cases are selected as good examples of neuronitis. In two of the cases pathologic reports are given.

CASE 1.—*Typical case of neuronitis: history of preceding infection; latent period; neuronitis; complete recovery.*

A girl, aged 6 years, in February 1934 had a mild illness of two weeks' duration in which there were low grade fever and a slight scaling of the skin (scarlet fever?). In the latter part of April the parents noted slowness and weakness in the child's gait. By the middle of May this weakness had increased in the legs and a similar weakness had appeared in the arms. The child complained of some pain in the back and aching in the knees. By June 1 she could hardly stand; she was unable to feed herself because of weakness of the arms.

Examination on June 10 did not show involvement of the cranial nerves. There was marked generalized muscular weakness; this was most profound in the legs. The arm reflexes were difficult to obtain; the deep leg reflexes were absent. The patient complained of some subjective numbness of the hands and feet, but no objective sensory changes could be made out. Joint and vibration senses were normal. Sphincteric control was not affected. Examination of the spinal fluid showed a positive reaction for globulin, 1 lymphocyte per cubic millimeter and 200 mg. of total protein per hundred cubic centimeters; the Wassermann reaction was negative. During the period of observation there was slight fever, but the temperature did not exceed 99 F. Convalescence was slow, but by Nov. 8, 1934, the report from the family physician stated that the child had recovered completely.

CASE 2.—*Neuronitis with choked disks, complete recovery.*

A housewife, aged 25, registered at the clinic on March 6, 1934. She stated that she had been well until a month previously. She had had no previous infec-

tion, although her family had recently passed through an epidemic of "colds." On February 6 severe occipital and frontal headaches set in, and they continued daily until admission to a hospital on February 12. There, spinal puncture afforded temporary relief. At about the same time that the headache began the patient noticed numbness and tingling in the fingers and feet, which progressed upward as far as the hips and wrists and were accompanied by some diminution in sensation in these regions. On February 24 weakness of the extremities, more marked in the legs, was first noticed. This came on gradually and grew progressively worse. At about that time also the patient complained of some difficulty with near vision and occasionally of diplopia. On March 6 she was admitted to the clinic.

General examination on admission gave negative results; neurologic examination, however, gave the following positive findings: There was slight facial weakness. Strength was graded —2 to —3 in the upper extremities and —4 in the lower extremities, except for the flexors and extensors of the toes and the tibial and peroneal muscles; in these weakness was not quite so extreme. (Grade —1 represents the least degree of impairment; grade —4 represents complete paralysis.) Sensations of pain, temperature and touch were decreased over the extremities, being about from 60 to 65 per cent (grade —2 to —3). Vibratory sense was grade —3 to —4 over the pelvic joints and from there down. Joint sense in the lower extremities was completely absent. The deep reflexes in the upper extremities were diminished 75 per cent, and in the lower extremities they were completely absent. All the abdominal reflexes were likewise absent. Plantar response was slightly flexor. Because of weakness, coordination in the upper extremities was impaired. Examination of the ocular fundi on March 7 revealed acute choking of the disks of 3 diopters on the right and of 2 diopters on the left. Objectively, vision was normal. The right pupil was slightly larger than the left.

Of the laboratory procedures carried out, examination of the spinal fluid alone revealed any abnormality. On the day of admission there were a positive reaction for globulin and pleocytosis, the count being 13 large lymphocytes and 11 polymorphonuclear leukocytes and a few erythrocytes. The total protein content of the spinal fluid was 400 mg. per hundred cubic centimeters. On subsequent examinations of the spinal fluid the pressure was found to be somewhat elevated, the highest being 33 cm. of water. Lange's colloidal gold test revealed a midzone curve. It is of interest that prior to the patient's admission to the clinic she had undergone six spinal punctures and that examination of fluid withdrawn at each of these punctures had shown the cell count to be 6 and the total protein content 150 mg.

The patient's stay in the hospital was marked by gradual but steady improvement. At no time did the temperature rise above normal, except as a result of typhoid vaccine therapy. In addition to this, treatment consisted of repeated spinal punctures, application of hot packs, administration of sedatives and general supportive measures.

On dismissal, on April 12, 1934, the patient's strength had improved to the point where she could stand alone and walk for a short distance. The total protein content of the spinal fluid had dropped to 120 mg. per hundred cubic centimeters. The choked disks, after an initial increase to a level of from 3 to 4 diopters, had receded to 3 diopters in both eyes. A letter from her physician in October 1934 informed us that she had made a complete recovery, including complete recession of the papilledema.

Unfortunately, the favorable outcome in the first two cases was not duplicated in the cases of the following two patients:

CASE 3.—*Neuronitis with facial diplegia; rapid progression; death. Pathologic changes.*

A farmer, aged 52, was brought to the clinic on Jan. 10, 1935. Seven weeks previously he had suffered an attack of "intestinal flu," during which he was beset with gripping abdominal pain and diarrhea. Two weeks later a sudden and severe neuralgic pain appeared in the right side of the head, face and neck. Three days later vesicles were visible on the right side of the scalp and face down to the level of the superciliary ridge. A few days after the onset of the facial pain the patient began to complain of pain in both shoulders, which was projected down into the arms. One or two days later a bandlike pain or discomfort became evident around the body at the level of the umbilicus. At about this time also the posterior aspect of the thighs and the lateral surface of the legs became painful, and this symptom was accompanied by numbness in the legs and feet and a feeling that control of them was faulty. The pain in the face and shoulders continued, although it was much milder. For three weeks before admission the right side of the forehead and the lower left side of the face had felt numb, and for the same period the left side of the face had been gradually flattening, so that the mouth had noticeably pulled to the right during the last few days before admission.

General examination revealed little information of special consequence. Neurologically, there was bilateral facial palsy, graded —4 on the left and —3 to —4 on the right. Speech was dysarthric. Along the distribution of the ophthalmic division of the fifth nerve all forms of sensation were diminished, being —2 to —3. The patient's gait was ataxic, and coordination was impaired. The deep reflexes of the arms were slightly increased. The patellar and achilles tendon jerks were obtained with great difficulty. There was some subjective numbness of the legs. The muscles of the legs were tender, and the patient complained of pain over the lower portion of the back and over the buttocks. Vibration sense was slightly diminished in the legs. Examination of the eyes on January 12 revealed a number of small corneal scars on the right; these were judged to be the result of previous herpes. The fundi were normal.

As in the previous case, the only laboratory procedure that revealed anything of significance was the examination of cerebrospinal fluid. On January 12 the cell count was 2 lymphocytes, the Nonne test for globulin was positive and the total protein content was 180 mg. per hundred cubic centimeters. One week later, on January 19, the total protein content had increased to 240 mg. On February 6 there were 2 small lymphocytes present, but the protein content by this time had reached a level of 500 mg.

During the patient's stay in the hospital his condition became steadily worse, although his temperature remained normal except after typhoid vaccine therapy. On January 19, nine days after admission, definite anesthesia of the hands, legs and feet was noted. Strength in the legs had greatly diminished. On the other hand, strength in the facial muscles had somewhat improved. The patient complained considerably of pain in the lumbar portion of the back, radiating into the left portion of the abdomen and down both legs. He was given a diet with high vitamin content, typhoid vaccine intravenously and daily physical therapy in the form of baking. On January 28 the arms as well as the legs were weak. By February 9 anodynes were necessary to relieve the severe pain. The next evening respiration was somewhat embarrassed, and this was accompanied by an accumulation of mucus and by cyanosis. Artificial respiration by the Drinker apparatus was resorted to at this time and some relief was obtained. On the morning of February 11, however, the patient was unable to swallow, and nasal feedings were necessary. At noon, pulmonary edema was marked. The patient died that afternoon.

Pathologic Observations.—No gross changes of any importance were noted at necropsy except beginning bronchopneumonia of both lungs, which was confirmed by microscopic examination.

The tissue was fixed in dilute solution of formaldehyde U. S. P. (1:10). Cross-sections and longitudinal sections were cut from the sciatic and femoral nerves, the brachial plexus and the sympathetic nervous system. Sections were also taken from numerous parts of the central nervous system, from the gasserian and dorsal root ganglia and from cranial nerves as well as from the phrenic and intercostal nerves. Microscopic study of the various peripheral nerves revealed fairly uniform changes with the various staining methods employed. Cross-sections of the sciatic nerves stained with hematoxylin and eosin showed marked swelling of the nerve bundles and edematous connective tissue separating the fibers. There was an increase in the number of Schwann cells and an apparent increase in the tissue between individual myelin sheaths. There were several small collections of lymphocytes but no plasma cells or polymorphonuclear leukocytes. The walls of some of the arterioles were much thicker than normal and were hyalinized. The interstitial tissue between the nerve bundles did not contain any cells denoting an inflammatory reaction, but the walls of the blood vessels were thickened; however, the degree of thickening was not as great as that in the smaller vessels in the nerve bundles. Longitudinal sections of the sciatic nerves stained with hematoxylin and eosin showed changes similar to those seen in the cross-sections (fig. 1). There was well marked proliferation of the Schwann cells, but this was not uniform. There were several small collections of lymphocytes and also some histiocytes containing blood pigment. There was an increase in the density of connective tissue between the nerve bundles, and here also there were collections of lymphocytes but no polymorphonuclear leukocytes. There were also a few lymphocytes in the sheaths of the nerve bundles. Weigert's stain for myelin sheaths and a modification of the Mallory-Heidenhain stain were used to demonstrate the myelin sheaths. These stains revealed marked diminution in the number of myelin sheaths present; some showed much more destruction than others. This patchy destruction varied from almost complete disappearance of stainable myelin sheaths, especially in some of the smaller bundles, to some bundles that were almost normal. The more finely myelinated fibers for the most part showed greater destruction. The longitudinal sections of the nerves in places showed active degeneration of the myelin, as represented by swelling, beading and fragmentation. This was seen better in sections stained by the Marchi method and with sudan III. With these stains active degeneration was seen to be marked (fig. 2), and some histiocytes containing droplets of fat were present. With the Mallory-Heidenhain stain the edema of the tissues was well demonstrated. This stain also indicated that thickening of the walls of the blood vessels was due to connective tissue, and this was confirmed with the Van Gieson stain. Stains for amyloid and paramyloid were also made, but neither of these substances was present. The Weigert stain for myelin sheaths in the longitudinal sections of the nerves showed that many areas were completely devoid of myelin sheaths; in others, the number of myelin sheaths was greatly reduced. In some of these areas histiocytes were seen containing myelin débris, and there were also some lymphocytes but no polymorphonuclear leukocytes.

The modified silver impregnation method revealed active degeneration of the axis-cylinders. In the sciatic nerves the swellings and beadings were much more pronounced, so that some of the nodules were many times the diameter of normal fibers; this was also associated with vacuolation of the degenerating axons.

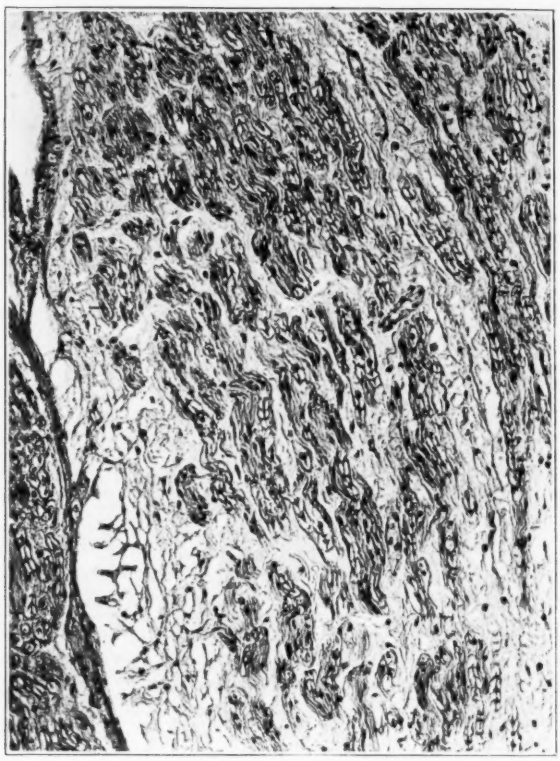

Fig. 1 (case 3).—Section of the right sciatic nerve, showing marked edema of the nerve producing separation of the fibers (hematoxylin and eosin; × 95). The absence of inflammation may be noted.

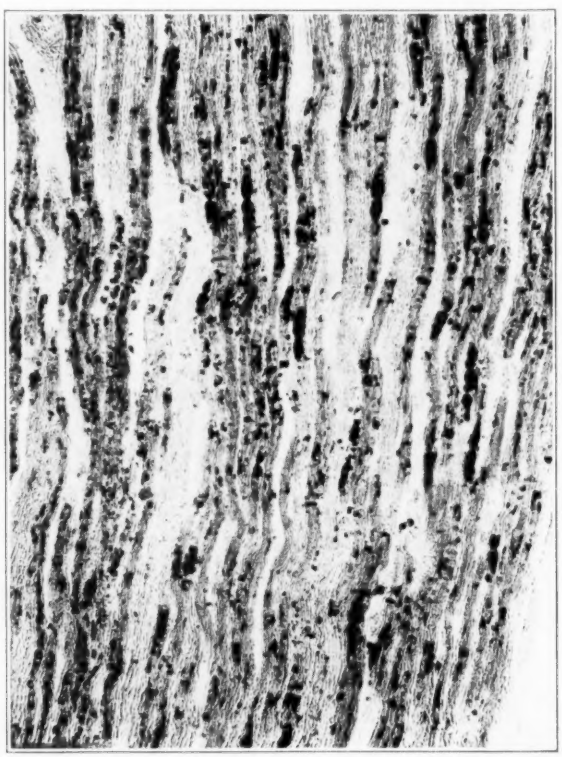

Fig. 2 (case 3).—Section showing active degeneration of myelin sheaths of the right femoral nerve (Marchi method; × 95).

Fragmentation of the axis-cylinders was marked in some bundles; the fibers were broken into small pieces which were curled into small rounded lumps. Some fibers were divided into several filaments which had the appearance of attempted regeneration. When this method of demonstrating axis-cylinders was combined with application of the sudan III stain for fat, the associated active degeneration of the myelin and axis-cylinders was beautifully demonstrated. It also showed that in some nerve bundles the axis-cylinders and myelin sheaths were almost all normal whereas in other bundles more than half of these structures were undergoing degeneration. With the hematoxylin and eosin stain, the femoral nerves evidenced less inflammatory reaction than the sciatic nerves. The degree of edema of the various nerve bundles varied greatly; some bundles showed none, and others showed edema even more markedly than in the sciatic nerves. The blood vessels had thickened hyalinized walls, but they were not so thick as in the sciatic nerves. In the longitudinal sections proliferation of the Schwann cells was pronounced. Edema was the most noticeable feature in contrast to the lack of evidence of inflammation (fig. 1). In several of the perivascular spaces in the connective tissue between nerve bundles there were large collections of lymphocytes. The stains for myelin sheaths showed changes almost identical with those seen in the sciatic nerves; in some of the small nerve bundles there was almost complete disappearance of the sheaths. The silver impregnation method for axis-cylinders showed that degeneration of these cylinders was also active and in some of the bundles quite extensive, so that practically no normal fibers remained. Changes were observed in the brachial plexus similar to those seen in the sciatic and femoral nerves.

In the few intercostal nerves examined changes were observed which were even more advanced than those in the nerves of the limbs; lymphocytes were more numerous, but still no polymorphonuclear leukocytes were seen, and there was marked edema of the interstitial tissue. The blood vessels did not have thickened walls. The stains for myelin sheath indicated that there was scarcely a normal myelin sheath in any of these nerves. The majority of the sheaths were swollen, beaded and fragmented (fig. 3), although a few retained their normal appearance. The silver impregnation method showed that similar degeneration was taking place in the axis-cylinders. This degeneration was advanced, but, on the other hand, attempted regeneration was also marked. The changes in the phrenic nerves were similar to those seen in the intercostal nerves, except that degeneration was less marked and signs of inflammation were absent. Changes in myelin sheaths and axis-cylinders were earlier than most of those observed in other nerves.

Sections of the dorsal root ganglia from different levels all showed somewhat similar changes. Scattered throughout the ganglia there were numerous lymphocytes; these occurred sometimes in islands but more frequently were scattered in a diffuse manner. No polymorphonuclear leukocytes or plasma cells were present. There was diffuse edema of the connective tissue, but this did not involve the nerve bundles in the ganglia themselves. In the nerve bundles going from the ganglia to the spinal cord there were few lymphocytes and little edema, but in the bundles distal to the ganglia there were collections of lymphocytes, and many were also scattered diffusely throughout the connective tissue which presented marked edema. The blood vessels were normal. In the distal nerve bundles there was an increase of the Schwann cells, but this was not true of the proximal bundles. Thionine stains showed that most of the ganglion cells were within normal limits for a patient of this age. There was no increase in the ectocapsular cells, and in only a few instances was there a slight proliferation of the endocapsular cells. Silver impregnation for ganglion cells and axis-cylinders showed

that most of the ganglion cells were outlined in a normal manner and that most of the axis-cylinders of the distal nerve bundles were fragmented, beaded and swollen, whereas those of the proximal nerve bundles were almost normal.

Sections from various levels of the spinal cord stained by all available staining methods showed them to be normal. The brain stem, cerebellum, basal nuclei and cerebrum were also normal. Sections through the level of the nucleus of the third nerve and that of the seventh nerve revealed mild chromatolysis. Sections of the seventh nerve showed early degeneration of some of the myelin sheaths;

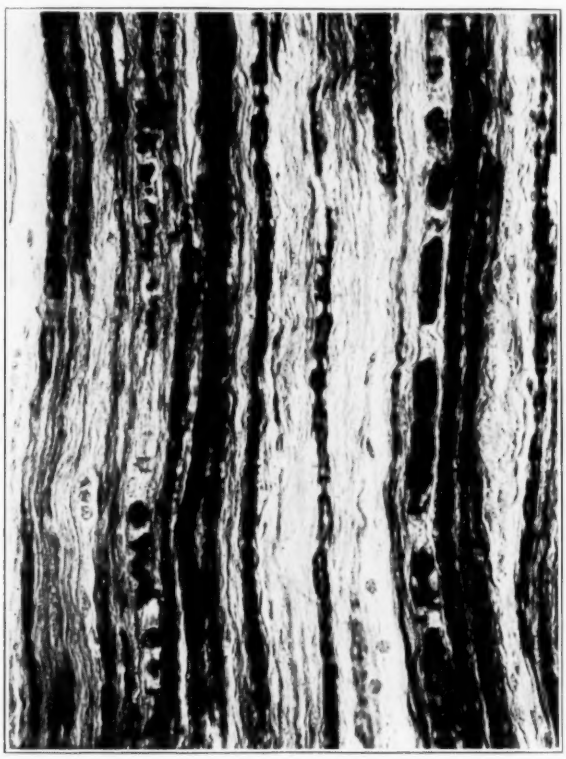

Fig. 3 (case 3).—Section showing beading and fragmentation of degenerating myelin sheaths of an intercostal nerve (stain for Weigert's myelin sheaths; × 215).

this was early and slight, and there was no inflammatory reaction and no edema. The degeneration of axis-cylinders was also slight. The third nerves showed no degeneration with the stains for myelin sheaths, but there were some lymphocytes scattered diffusely through the nerves, and the myelin sheaths were separated from each other by edema. The blood vessels were normal. The silver impregnation method for axis-cylinders showed early degeneration with irregular swellings and fragmentation. The optic nerves were normal, as well as the remaining cranial nerves examined except the fifth. Both gasserian ganglia showed changes similar to those observed in the dorsal root ganglia, except that the inflammatory changes were more marked (fig. 4). There were many polymorphonuclear leukocytes in

addition to the lymphocytes. The inflammatory cells in the ganglia were numerous. These cells had infiltrated the connective tissue and the nerve bundles in the ganglia. In addition to the leukocytic infiltration there was excessive edema of the connective tissue of some of the nerve bundles. There was no proliferation of the ectocapsular or endocapsular cells, and most of the ganglion cells were normal. This was confirmed by various staining methods. The silver impregnation method revealed that most of the axis-cylinders between the brain stem and ganglia were normal, but those distal to the ganglia had undergone and were

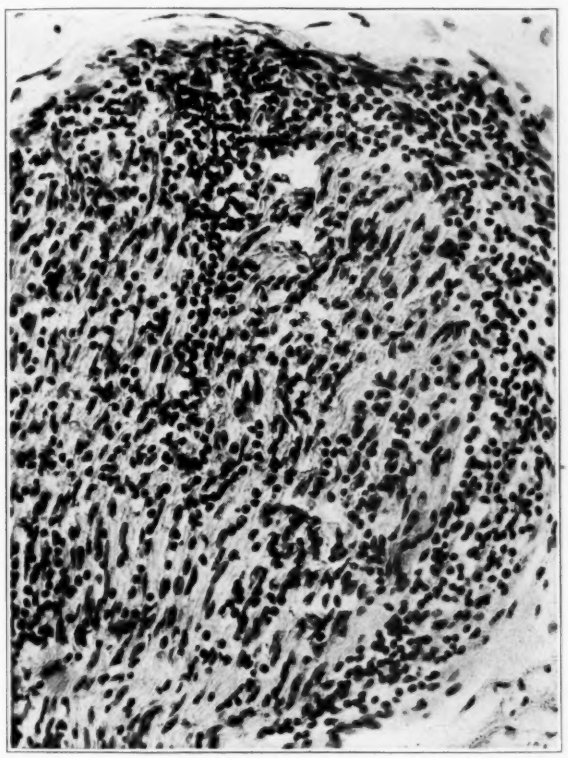

Fig. 4 (case 3).—Section of the fifth cranial nerve just distal to the gasserian ganglion, showing a marked subacute inflammatory process (hematoxylin and eosin; × 205). Most of the cells are lymphocytes; few polymorphonuclear leukocytes are present.

undergoing degeneration which was characterized by extensive beading, swelling, vacuolation and fragmentation (figs. 5 and 6). There was also quite definite evidence of regeneration, especially in the nerve bundles close to the ganglia themselves. The blood vessels were normal.

The sympathetic nervous system was also studied, but there were no changes except those that might be accounted for on the basis of the patient's age.

CASE 4.—*Neuronitis complicated by Hodgkin's disease; fatal termination.*

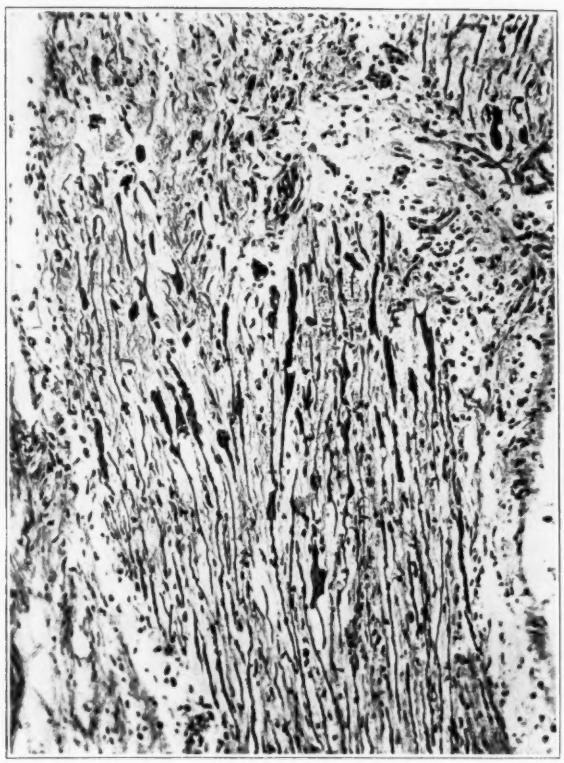

Fig. 5 (case 3).—Section of a nerve distal to the gasserian ganglion, showing active degeneration of axis-cylinders evidenced by beading, swelling and fragmentation (modified silver impregnation method; × 115).

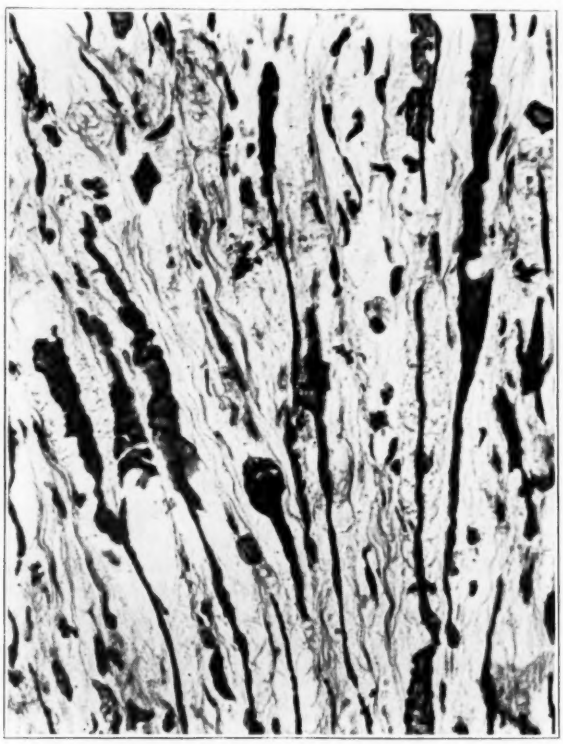

Fig. 6 (case 3).—Higher magnification (× 365) of figure 5, showing the fragmentation and vacuolation of the axis-cylinders better. In several places minute fragments of axis-cylinders can be seen.

A man, aged 28, came to the clinic in January 1931, complaining of exhaustion and loss of weight. Shortly before admission he had noted soreness and numbness in the hands and feet.

A roentgenogram of the chest revealed a large mediastinal mass. After biopsy of a cervical lymph node a diagnosis of lymphosarcoma of Hodgkin's type was made. The patient was given roentgen treatments, and by June 17, 1931, examination gave negative results and the numbness had disappeared. Treatment was continued and the patient felt well.

In September 1934 the patient observed increasing weakness and some tenderness in the legs. Roentgenograms of the chest and entire spinal column showed normal conditions. Blood smears also gave normal results. Another course of roentgen therapy was given, but the weakness increased.

Neurologic examination on Oct. 30, 1934, revealed marked motor weakness, especially in the legs. The arm reflexes were diminished, and the patellar and achilles tendon reflexes were absent. There was a suggestion of plantar extension in both feet. Vibration sense in the legs and hips was practically absent. Joint sense was but slightly altered. Subjectively the patient complained of numbness of the legs that extended up to the waist. The hands were also numb up to the wrists. Objectively there was a slight change in the feet, about grade —1. Examination of spinal fluid showed a negative Kolmer reaction, a positive Nonne reaction and a total protein content of 100 mg. per hundred cubic centimeters; there were 16 small lymphocytes per cubic millimeter and a midzone colloidal gold curve. The physical properties were normal.

The patient gradually became weaker, so that by Jan. 1, 1935, he had almost complete motor palsy of all four extremities. He then slowly began to improve as far as motor power was concerned, but diarrhea and loss of appetite developed, and herpes zoster appeared over the lower portion of the chest. He died on April 11, 1935.

The reason for reporting this case is that we are able to present the pathologic observations. We realize the complication that exists and the difficulty of proving that this represents a case of neuronitis. We believe that the two conditions were unrelated, and we know that there was no extension of the Hodgkin's disease into the nervous system. It is also known that roentgen therapy in itself does not produce such changes in the nervous system. The infrequency of pathologic study in these cases would alone justify their presentation.

Pathologic Observations.—The lymph nodes in the mediastinum and hili of the lungs, as well as those in the abdominal cavity, were much enlarged and firm. This was particularly noticeable around the abdominal aorta, where they were matted together to form a large, elongated firm mass that stretched from the celiac axis to the bifurcation. The tumor had invaded the spleen, producing splenomegaly (the spleen weighed 570 Gm.), and had also invaded the liver, lungs and kidneys. The immediate cause of death was general peritonitis of indeterminate origin; it might, however, have originated in a small abscess in the left kidney. The process had not invaded any of the bones; in the examination particular attention was paid to the vertebrae and pelvic bones. The spinal cord and major nerve trunks were free from invasion by the tumor. The spinal cord seemed to be normal and was not compressed at any point, although the larger nerve trunks were enlarged and edematous. The body had been prepared immediately after death by injection of solution of formaldehyde into the blood vessels, and the tissues removed were further fixed in dilute solution of formaldehyde U. S. P. (1:10).

Microscopically, the tumor proved to be a typical Hodgkin type of sarcoma, although it had not invaded the bones, the spinal canal, the spinal cord, the nerve roots or the nerve trunks.

As many staining methods as possible were carried out on the tissue fixed in solution of formaldehyde. Hematoxylin and eosin stains disclosed that there was no inflammatory reaction in the sciatic and femoral nerves or in the brachial plexus. In all these nerves there was marked edema of the supporting tissues (fig. 7). In this respect they resembled those described in case 3; otherwise however, they differed in that there were no traces of inflammation, even lympho-

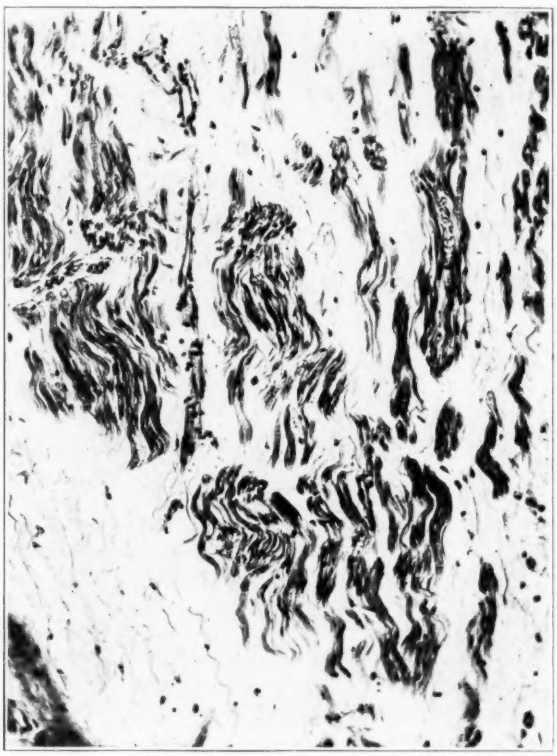

Fig. 7 (case 4).—Section of the femoral nerve, showing extensive edema but no inflammation in the nerve bundle (hematoxylin and eosin; × 100).

cytes being absent. In some nerve bundles there was a marked increase in the nuclei of the Schwann cells. Weigert's stain for myelin sheaths and a modification of the Mallory-Heidenhain stain showed that many of the myelin sheaths were normal but that there were some bundles and groups of fibers in which degeneration was extensive and that in a few bundles there was complete disappearance of myelin sheaths (fig. 8). The stains for fat gave some evidence of active degeneration, but this was much less than was present in the previous case. With the silver impregnation method for axis-cylinders it was seen that a few fibers were undergoing degeneration, but in contrast to the previous case there was much

more evidence of regeneration. This regeneration was evidenced by two or more irregular filaments projecting from the ends of slightly swollen axis-cylinders. These filaments did not always arise from the end of the nerve fibers but projected irregularly from the axon near its termination and followed an irregular tortuous course, so that it was difficult to follow them for any distance into the surrounding tissue. We could not be certain that we saw cones of growth. The blood vessels in and around the nerves were normal for a patient of that age.

Microscopic examination of the dorsal root ganglia did not show any acute inflammatory changes. The fifth and sixth thoracic ganglia on the left side cor-

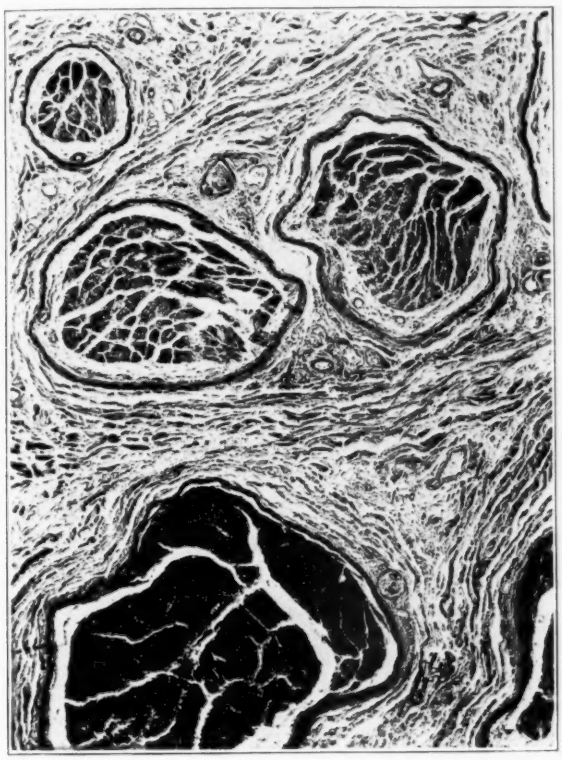

Fig. 8 (case 4).—The top three nerve bundles show almost complete degeneration of myelin sheaths, while the lower bundle is almost normal (Weigert's stain for myelin sheaths; × 50).

responding to the distribution of the herpes zoster did not contain any polymorphonuclear leukocytes and were similar to the others examined. In spite of the fact that there were no inflammatory cells present in any of the dorsal root ganglia, changes in some of the ganglion cells were marked. There was an apparent increase of the interstitial cells, and some small circumscribed collections of cells that resembled lymphocytes were seen. The thionine stain indicated that some of the remaining ganglion cells were normal, but most showed varying degrees of change. Chromatolysis or pyknosis was not present, but the margins of some

of the cells seemed to be frayed, some contained numerous vacuoles, giving the cells a foamy appearance, and some had almost completely disappeared. There was little pigment present in any of the cells. There is no specific or satisfactory stain available to demonstrate the bodies of the endocapsular cells, but with hematoxylin and eosin the ectocapsular cells seemed to be almost normal; only occasionally had these cells increased in numbers. The most profound change was noted in the endocapsular cells, which showed varying degrees of proliferation and hyperplasia (fig. 9). All stages of this proliferation were visible in different parts of the various ganglia examined, and in some of the ganglia the nerve cells

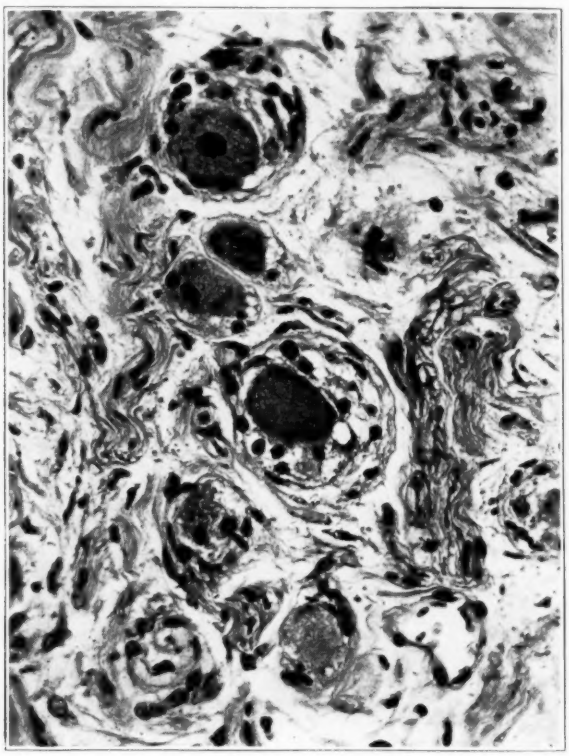

Fig. 9 (case 4).—Section from a dorsal root ganglion, showing extensive proliferation of the endocapsular cells compressing the ganglion cells, some of which have partly degenerated (hematoxylin and eosin; × 275). The absence of inflammation may be noted.

had disappeared only to be replaced by proliferated endocapsular cells that completely filled the space formerly occupied by the ganglion cells (fig. 10). It was impossible to be sure whether proliferation was the cause of degeneration of the ganglion cells or the result of their disappearance; in some places it seemed as if the ganglion cells had disintegrated and the endocapsular cells had proliferated to occupy the space, whereas in other places the opposite seemed to be true. There were no ordinary inflammatory cells in the ganglia, especially at the site of capsular cell proliferation.

The nerve roots entering and leaving the dorsal root ganglia showed less edema than the peripheral nerves, but here occasional lymphocytes were present, not as groups but separately. The nerves peripheral to the ganglia showed the regeneration better than was observed elsewhere in the peripheral nervous system.

Microscopic examination of the spinal cord revealed that the cells of the anterior horns were normal at all levels but that there was an increase in the number and size of the astrocytes, especially in the posterior columns. There was no inflammatory reaction anywhere. The meninges were normal. Weigert's stain for myelin sheaths showed that there was some degeneration of the myelin sheaths.

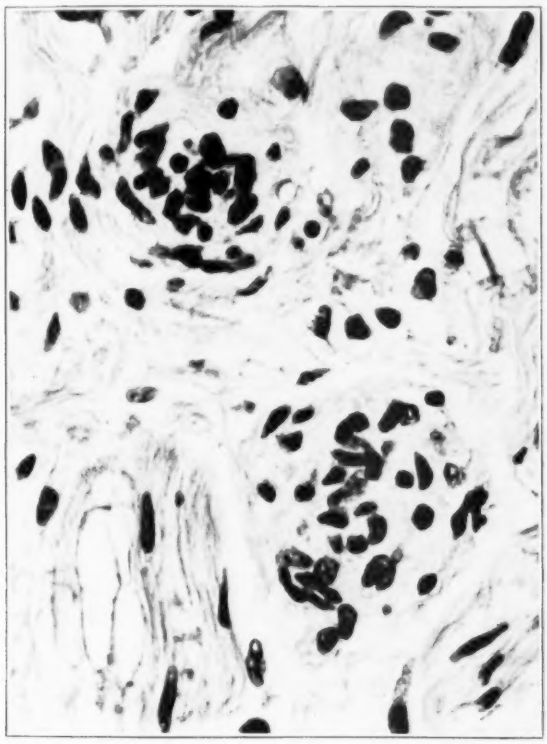

Fig. 10 (case 4).—In this section of the dorsal root ganglia the endocapsular proliferation has now been completed with the disappearance of the ganglion cells (hematoxylin and eosin stain; × 525).

This was well marked in the lumbar region where the lesion was limited to the posterior columns, whereas in the thoracic region the degeneration was less pronounced in the posterior columns, although it had to a minor extent involved all columns. In the thoracic region there was some gliosis in the middle of the posterior columns; this gliosis diminished in the lower levels, so that it was slight at the lumbar and sacral regions. It was unfortunate that the brain could not be obtained for microscopic examination.

In the series of fifteen cases not included in the table there was one death. As in that case there were pathologic changes similar to those in the two cases just reported, we shall refer to it briefly.

CASE 5.—*Neuronitis; fatal termination.*

A man, aged 50, fourteen weeks before admission to the clinic on July 25, 1932, had an attack of abdominal pain and distention associated with pain and progressive weakness of the legs and arms. On examination there was weakness of the facial muscles and of the legs and arms. All the deep reflexes were abolished. Chemical examination for arsenic, lead and thallium gave negative results. A diagnosis of facial diplegia with polyneuritis had previously been made, and the spinal fluid was stated to have been normal. The patient died six days after admission, on July 31.

Pathologic Observations.—At necropsy no gross lesion was noted except enlargement of the heart, with chronic infarction (fibrosis) of the myocardium. Microscopic examination of the peripheral nerves gave evidence of extensive degeneration of the myelin sheaths and axis-cylinders associated with edema of the nerve bundles and absence of inflammatory reaction. The degeneration was of recent origin, as there was active degeneration of both the myelin sheaths and the axis-cylinders but no evidence of regeneration. There were some scavenger cells present in some of the nerve bundles. The most extensive change was present in the blood vessels, in the nerve bundles and in the interstitial tissue surrounding the bundles. These arteries and arterioles had markedly thickened walls with narrowed lumens; this seemed to us to be a possible explanation of the degeneration of the nerve tissue. The thickened walls had a peculiar lumpy appearance and stained specifically for amyloid with the congo red, bismarck brown and gentian violet stains. There was no history of chronic suppuration of any infectious process which could explain the presence of the amyloid in the walls of the arteries and arterioles.

COMMENT

From a study of our material it appears that there is a group of cases of polyneuritis that may be brought together under a separate heading, such as neuronitis. As has been suggested by Cobb and Coggeshall, the disease in some of these cases may be of virus origin; however, it is not known whether this syndrome of neuronitis is characteristic of a condition due to virus or if it may be produced by other agents, such as bacteria, toxins and chemicals. Cobb and Coggeshall gave a list of about thirteen diseases due to virus which may produce polyneuritis. From our observations we have no way of determining the exact etiology. In only one case was there a recognizable condition due to virus, and that was herpes. Herpes did occur in another case, but this was after the onset of the neuritic symptoms. In the remaining cases the preceding illness was in the nature of a cold, grip or mild fever; in a small percentage of the cases no apparent preceding febrile condition was recognized.

It may be unwise to attempt any positive deductions from our clinicopathologic studies, but the impression is forced on us that we

are dealing with a condition due to a virus that in the present instance has a predilection for the peripheral neurons. It is true that at times the pathologic process is not limited to the peripheral nerves but may spread to the spinal cord or even to the brain. That these syndromes may represent the various manifestations of a single virus is not beyond the realm of probability, although we have little proof for such a statement.

While the clinical picture is fairly uniform, variations do occur. At times the course of the illness is mild and of short duration; it may, however, be severe and result in death. Involvement of the cranial nerves, indicated by bilateral facial palsy, is not unusual, and its presence does not merit a special classification. Choked disks are rare but do occur.

To designate the condition in this group of cases as neuronitis is not our purpose in this paper. It does appear, however, that the term is sufficiently descriptive and in lieu of a better one might well be applied to the disease in this group.

There is no need to review the symptoms in our series of cases, as the clinical syndrome is well recognized. It is of interest that examination of the spinal fluid gave fairly uniform results. We are not certain that these findings are an essential criterion for the diagnosis of neuronitis, but it is interesting that in every instance the total protein content was well above normal and that frequently it was above 200 mg. per hundred cubic centimeters of fluid. The amount of sugar and chlorides in the spinal fluid was normal.

As was stated previously, we had in addition to the twenty cases a series of fifteen in which we believe that the disease belonged in the same category. In the latter series either we saw the patient during the period of recovery and did not carry out a study of the spinal fluid or we saw him at a time prior to that when routine determinations of total protein were made. In any event, in these thirty-five cases the condition appears to us to belong to the same category. As has been said, there was one death in the series of fifteen cases, giving a mortality of 14 per cent for the entire series of thirty-five cases.

The possibility that some of our cases belong to the "bacteriotoxic" group of cases of polyneuritis cannot be disputed. We also realize the difficulty of differentiating so-called cases of neuronitis of metabolic or "deficiency disease" origin and have therefore avoided including such cases in our series. Chemical analysis for arsenic and lead was carried out in only a few of our cases, but it seems fair to assume that none of our cases represented instances of chemical polyneuritis.

In the three cases studied pathologically, degeneration was limited to the peripheral nerves, and although in case 4 there were changes in

the spinal cord, these were slight and ascending in nature. The ganglion cells of the anterior horns of the spinal cord were normal, and there was no degeneration in the nerve roots within the spinal canal. The changes in the nerve trunks were those of degeneration, but no inflammation was present. The most obvious abnormality was edema in the nerve bundles, which was so pronounced that it was noted grossly. There were a few lymphocytes in the nerves in case 3, but it seemed to us that these could be accounted for on a basis of degeneration rather than of true inflammation. Regeneration was very slight in case 3, but in case 4 it was well marked. One notable observation was that the degenerative changes were not uniformly distributed throughout the nerve trunks but that some bundles were more degenerated than others. The dorsal root ganglia and gasserian ganglia in case 3 showed the only obvious inflammatory reaction; yet at this stage the ganglion cells were practically all normal. In case 4 there was no inflammatory reaction in any of the ganglia. The patient had had neuronitis for about five months before he died, and his death was not attributable to the neuronitis. The changes in the dorsal root ganglia were extensive, but the interpretation of such changes is difficult. Many of the ganglion cells had degenerated and disappeared or were in the process of degeneration. It was impossible to decide whether the proliferation of the endocapsular cells was the cause or the result of this degeneration. It is quite possible and even probable that endocapsular cell proliferation is entirely independent of the neuronitis; yet in case 3 there was some, although slight, proliferation. It is to be regretted that we have no available staining method that demonstrates clearly the endocapsular cells of the dorsal root ganglia. In case 3 the nuclei of the third and seventh cranial nerves showed chromatolysis, but the cells were not destroyed and there was no inflammation in these nuclei. The nuclei of the other cranial nerves were normal.

As was stated in the opening paragraph of this paper, our interest in this subject was aroused by the apparent increase in the occurrence of these cases, eight of the twenty cases having been encountered in 1934. Whether we are dealing with a specific disease entity or merely with a clinical syndrome due to various causes remains a problem for added study.

SUMMARY AND CONCLUSIONS

There appears to be a group of cases of polyneuritis which may be designated as instances of neuronitis. The disease is characterized by a history of preceding illness, by a latent period of well-being, and finally by the development of polyneuritis. Involvement of cranial nerves, as facial palsy, may occur. Choked disks are occasionally present, and at times signs of involvement of the cord can be demonstrated.

The results of examination of the spinal fluid are of diagnostic value, there being, as a rule, an increase in the total protein content with but slight change in the cell count.

Recovery is the rule; in our series of thirty-five cases the mortality was 14 per cent.

Pathologically, there is patchy degeneration of myelin and fragmentation of the axis-cylinders of the peripheral nerves, without any evidence of inflammation.

From our observations the number of cases of this type of polyneuritis appears to be on the increase.

DISCUSSION

Dr. Stanley Cobb, Boston: This work is especially interesting because the authors have had so large an experience, larger than I have had. I have had more cases of this type in recent years, but if one looks back to the work of Osler in 1892 and of Willis Taylor more recently it appears that there have always been scattered cases of this disease. I think that the patients have usually more atrophy in the affected muscles than was described by the authors. Also, according to the authors, the spinal fluid of all their patients showed a high total protein content; this has not been a regular finding in the cases which my co-workers and I studied. In over half of our cases there was a high protein content. It was enormously high now and then; for example, one patient had over 1,000 mg. of protein per hundred cubic centimeters of cerebrospinal fluid. Many had an almost normal protein content.

In our cases, as in the authors', there was ordinarily a moderate increase in the number of lymphocytes in the spinal fluid. I wonder, in relation to this, whether if one had been able to observe these patients earlier and longer all would not have shown fever, an increased number of lymphocytes and a high protein content of the spinal fluid. I remember that some of our patients had lymphocytosis and an increased protein content of the cerebrospinal fluid in the first weeks of the disease; later the fluid became normal. Therefore, one may reasonably compare this disease with anterior poliomyelitis. Almost all our patients with polyneuritis came under observation late in the disease. Perhaps that is why we failed to observe the changes in the spinal fluid.

Dr. LaSalle Archambault, Albany, N. Y.: How can the authors of this paper differentiate the disease they have just described from what was described in 1916 by Guillain, Barré and Strohl under the name of curable polyradiculoneuritis with albuminocytologic dissociation of the spinal fluid?

Dr. Adolph Meyer, Baltimore: I am sorry that Dr. Kennedy is not here, because it would be of interest to know just what is implied by the term neuronitis. After all, it is known that there are a number of conditions in which degeneration of nerve fibers is found without great evidence of any extraneously invading inflammatory factors. There are the toxic processes and avitaminosis, and in 1901, in describing so-called central neuritis, which was almost epidemic in the Worcester State Hospital, I dealt with a disorder to which one might also refer as a neuronitis, if one wanted to use that term to designate degeneration of nerve fibers with corresponding alterations of many of the nerve cells. In the cases which I have learned to associate with avitaminosis due to artificial feeding with inadequate attention to the composition of the feeding material the disturbance

was largely in the nerve cell bodies, but the nerve fibers were also involved. The point is this: Evidently in this disease, as in many of the disorders of the nervous system, there are quite a number of types of distribution (as, for instance, in the palsies due to lead poisoning) and of types of reactions; undoubtedly the reaction is not merely parenchymatous but may lead to a reaction in the interior tissue surrounding the nerve elements. To speak of neuronitis is a little awkward. One ought to have a term for the "primary" alterations of nerve elements. After all, when the condition is largely a nutritional affair it is awkward to speak of it as neuronitis.

With regard to examinations of the cerebrospinal fluid, I wish to say that formerly examinations of the spinal fluid were not made as they are now. I am convinced that in many cases in which the alterations are essentially parenchymatous one can find minor changes in the cerebrospinal fluid without having to think of dementia paralytica and similar conditions.

Dr. Louis Casamajor, New York: I share with Dr. Meyer the doubt as to what the term neuronitis means. Dr. Kennedy applied the term to a condition seen in the soldiers in France in 1917 and 1918. Clinically, the patients whom he observed showed a characteristic ascending paralysis that resembled that of Landry. On examination, there were flaccid paralysis and a definite anesthesia. The paralysis and anesthesia ascended well up into the cervical region; then in most cases it receded, and the patient recovered completely. I had the opportunity of securing the spinal cords from two patients with the disease, and the pathologic change was entirely in the arachnoid. There was little inflammatory change except in the arachnoid, but the changes there were marked. I wonder whether Dr. Moersch's cases were investigated with the changes in the arachnoid in mind.

Dr. Israel Wechsler, New York: The paper by Dr. Moersch, Dr. Kernohan and Dr. Gilpin proves, if further proof is necessary, that the whole subject of polyneuritis must be rewritten. The term "polyneuritis" is certainly not applicable to most of the conditions which have hitherto been described as polyneuritis. Aside from the fact that ectodermal tissue does not respond with an inflammatory process as does mesodermal tissue, it has rarely been shown pathologically that there is actual inflammation of the nerves in cases of polyneuritis due to alcoholism, lead poisoning, arsenic poisoning, diphtheria and so on. In all these conditions there is a degenerative process. Therefore, the term "polyneuritis" does not apply to them. Further, if the noxious agents by chance affect the central nervous system, more particularly the brain, they do not give rise to an inflammatory reaction. Lead gives rise to encephalopathy; so do alcohol and many other poisons. Therefore there is no reason to suppose that the toxin or other agent which happens to be operative should cause an inflammatory reaction in the peripheral nerves and encephalopathy if it affects the central nervous system.

The only exception to this are the cases reported by the authors of the paper. If the term polyneuritis is used, it should be applied only in cases in which there are fever and other evidences of inflammation. In other cases I think one is dealing with degeneration and avitaminosis. The absence of vitamins is one causative factor, in addition to alcohol, lead, phosphorus, arsenic, etc. I think that avitaminosis plays the ultimate and probably the decisive rôle. Whether this is true or not, only in cases in which an inflammatory reaction is present does the condition deserve the name polyneuritis. All neurologists have observed such cases since the epidemic of encephalitis in 1918 and 1919, and in subsequent pandemics. The loss of motor power and the occurrence of comparatively few atrophies are intelligible in lesions of the central nervous system. Most patients with true polyneuritis

have at one time or another fever and some degree of meningeal reaction, such as pleocytosis, increased protein content of the spinal fluid, etc. I think that the reaction shown in the cases reported is a little less severe than the one ordinarily observed. Therefore, I think that the name polyneuritis—not neuronitis, which is a barbarous word—should be applied in these cases and not in the others. I wonder whether the name peripheral neuropathy, comparable to encephalopathy or myelopathy, would be acceptable. It may fit better with the definition of terms.

Dr. Abraham Rabiner, New York: Several years ago Dr. Strauss and I read before this association a paper entitled "Myeloradiculitis." All the patients recovered, and pathologic study was impossible. I wish to cite one point in view of the discussion as to pathologic changes. About a year later one of these patients, a woman, returned to us with a picture typical of a postencephalitic parkinsonian syndrome. This and the fact that one of the authors' patients showed herpes zoster make me think that all the groups of diseases under discussion are caused by the same virus or infectious agent as that underlying the syndrome of epidemic encephalitis.

Dr. Irving Sands, Brooklyn: Has the sugar content of the spinal fluid been estimated in these cases?

Dr. Frederick P. Moersch, Rochester, Minn.: I realize that this is a difficult problem, and there is considerable theory connected with it. The real reason my co-workers and I studied our cases is, as we stated in the opening sentence of the paper, that it appeared to us that the number of cases of this condition has been increasing. We have seen cases of it since 1918, but in the past three years we have observed about fifteen cases. I doubt that this has occurred just because we are enthusiastic over the problem.

I believe that Dr. Cobb's statement is correct; if these cases were seen early, the spinal fluid might present a different picture. It is interesting that in several of these cases the total protein content and the cell count increased during the period of observation. In the patient whose photograph I showed, the protein content increased from 240 to 400 mg. per hundred cubic centimeters, and during the period of recovery it dropped to 120 mg. Therefore what the spinal fluid may show depends on when one sees these cases.

There is no question that there is some inflammatory reaction, but the inflammation is out of proportion to the degenerative character of the disease. That was the impression I wished to convey—not the idea that there was no evidence of inflammation.

Regarding the suggestion of Dr. Archambault, I think that it is correct. We did not examine the spinal fluid for sugar, hence I am unable to answer his question.

In summary, I believe that the number of cases of this condition is increasing; this is not only our own observation but that of other neurologists with whom we have discussed the problem. If one wishes to theorize a bit, one might agree with Dr. Rabiner that this form of polyneuritis is another manifestation of an infectious disease or of a condition caused by a virus which formerly presented itself as epidemic encephalitis.

There is no question that the term neuronitis is not a good one, but I believe that there is a definite category of cases that should be separated from the large group of cases of polyneuritis just as one separates cases of polyneuritis due to diphtheria, lead poisoning and alcoholism. Also neuronitis seems to me to be different from polyneuritis due to vitamin deficiency.

THE SYMPATHETIC NERVOUS SYSTEM IN MIGRAINE

NEGATIVE EFFECT OF ERGOTAMINE TARTRATE ON THE ELECTRICAL RESISTANCE OF THE SKIN DURING THE RELIEF OF MIGRAINE HEADACHE

PHILIP SOLOMON, M.D.

BOSTON

In recent years there has been a popular tendency in medicine to make sweeping and unwarranted generalizations regarding the activity of the sympathetic nervous system in a number of clinical conditions of obscure etiology. Terms such as sympathicotonia, vagotonia, autonomic dysfunction and the like are commonly used in the literature as a cloak for ignorance of the actual mechanism of the condition in question.

These remarks are particularly applicable to the problem of migraine, in which so many investigators recently have implicated the sympathetic nervous system in theories regarding the etiology of the disease.[1] These theories have been especially difficult to evaluate on account of the almost complete absence of evidence either for or against them. In spite of this situation, perhaps because of it, the theory of sympathetic dysfunction in migraine is becoming more widely accepted.[2]

The recent successful use of ergotamine in the relief of the individual attacks of migraine headache [3] has been easily explained to the satisfaction of the adherents to the theory of sympathetic dysfunction by the

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This investigation was aided in part by a grant of the Josiah Macy Jr. Foundation.

From the Neurological Unit, Boston City Hospital, and the Department of Neurology, Harvard Medical School.

1. (*a*) Blitzsten, N. L., and Brams, W. A.: Migraine with Abdominal Equivalent, J. A. M. A. **86**:675 (March 6) 1926. (*b*) Dandy, W. E.: Treatment of Hemicrania (Migraine) by Removal of the Inferior Cervical and the First Thoracic Sympathetic Ganglion, Bull. Johns Hopkins Hosp. **48**:357, 1931. (*c*) Hartung, E. F.: Present Day Aspects of Migraine, New York State J. Med. **27**:240, 1927. (*d*) Leischner, A. W.: Therapeutische Versuche bei Melancholie, Schizophrenie und Migräne, Med. Klin. **26**:1592, 1930. (*e*) Mackay, R. P.: Ophthalmoplegic Migraine, Am. J. Ophth. **12**:889, 1929. (*f*) Muck, O.: Ueber das Wesen der Hemicrania sympathicotonica, München. med. Wchnschr. **71**:1749, 1924. (*g*) Richter, H.: Zur Frage der Pathogenese des Migräneanfalles und seiner Beziehungen zum epileptischen Anfall, Ztschr. f. d. ges. Neurol. u. Psychiat. **97**:387, 1925. (*h*) Vallery-Radot, Pasteur: Rapport sur la pathogénie des migraines, Rev. neurol. **32**:881, 1925.

2. Riley, H. A.: Migraine, Bull. Neurol. Inst. New York **2**:429, 1932.

3. Lennox, W. G.: The Use of Ergotamine Tartrate in Migraine, New England J. Med. **210**:1061, 1934.

assertion that ergotamine paralyzes the sympathetic system.[4] But the pharmacologic work on which this statement is based was done for the most part on anesthetized animals, and the doses were far in excess of the amounts used in the treatment of migraine. No observations have been reported that demonstrate a depressing effect on the sympathetic nervous system of man. In fact, when ergotamine is given in the usual therapeutic doses many of its effects can be explained more easily by assuming that there is a moderate stimulation of the sympathetic system.[5]

The essential difficulties in this situation obviously arise from the lack of a suitable indicator to measure sympathetic activity. Observations of a number of clinical factors have been advocated for this purpose: (1) the heart rate, (2) the blood pressure, (3) the skin temperature, (4) the velocity of blood flow in the extremities, (5) the size of the pupils, (6) the ciliospinal reflex and the reaction to the pilomotor test and the skin stroke test and the like and (7) the reaction to drugs, e. g., the Goetsch test with epinephrine. The first four have the advantage of being susceptible to accurate measurement and continuous automatic recording, but the remainder are too difficult to quantitate to be of much experimental or clinical use. The tests utilizing the reaction to drugs have the additional disadvantage of not being able to follow rapid continuous changes. The serious objection to the procedures mentioned is that in all of them both sympathetic and parasympathetic activity must be taken into account, so that it is impossible by their use to determine the sympathetic activity alone.

The purpose of this paper is (1) to present a method for measuring sympathetic activity continuously and accurately by determining the electrical resistance of the skin and (2) to report the results obtained by applying this method to the study of the sympathetic nervous system of patients with migraine.

THE ELECTRICAL RESISTANCE OF THE SKIN

The electrical properties of the human body have been investigated chiefly with respect to the so-called psychogalvanic reflex, on which subject hundreds of papers have appeared in the medical and psychologic literature.[6] The physics and physiology of the psychogalvanic reflex have recently been reviewed in the light of the advances that have been made in the past few years.[7] The reflex consists in a decrease in the electrical

4. Trautmann, Edgar: Die Beeinflussung migräneartiger Zustände durch ein Sympathikushemmendes Mittel (Gynergen), München. med. Wchnschr. **75**:513, 1928.

5. Goldman, M., Jr.,: Recherches cliniques sur l'action de l'ergotamine sur le système végétatif, Arch. d. mal. du cœur **21**:204, 1928.

6. Landis, Carney, and De Wick, H. N.: The Electrical Phenomena of the Skin (Psychogalvanic Reflex), Psychol. Bull. **26**:64, 1929; **29**:693, 1932.

7. Solomon, Philip: The Psychogalvanic Reflex: Applications to Neurology and Psychiatry, Arch. Neurol. & Psychiat. **34**:818 (Oct.) 1935.

resistance over the palm or sole and depends on changes in the permeability of the cell membranes of the sweat glands.[8] These changes in permeability are brought about through the sympathetic nervous system, which abundantly supplies the sweat glands.[9] The intact sympathetic supply to the skin under the electrode is a necessary and sufficient condition for the production of the psychogalvanic reflex following an appropriate stimulus.[10] Stimulation of the sympathetic system uniformly causes a decrease in the electrical resistance, while inhibition causes a rise. These changes are likely to be more prolonged under certain conditions than those seen in the psychogalvanic reflex, so that it is more proper in this respect to speak of changes in the level of the electrical resistance than of the reflex alone.

Since the dependence of the electrical resistance of the skin on the sympathetic system has been recognized for some time, it is surprising that this method has been applied so little in problems involving sympathetic activity. Richter [11] has used this method in a study of sympathetic activity during sleep and again in a study of regeneration of the sympathetic nervous system after injury.[12] Schwartz [13] has used the method to demonstrate the presence of reflex activity solely within the sympathetic nervous system. It may be that other investigators have avoided the use of this method because of the many controversies that have arisen regarding its use in connection with the psychogalvanic reflex. But while the value of the psychogalvanic reflex in psychology and psychiatry has justifiably been called in question,[14] there seems to be no reason for doubting the validity of using the electrical resistance of the skin in studying the activity of the sympathetic nervous system.

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8. Darrow, C. W.: The Electrical, Circulatory, Secretory, and Thermal Reflexes of the Skin, Proc. Internat. Cong. Psychol. **9**:136, 1929.

9. Gildemeister, M.: Der galvanische Hautreflex als Teilerscheinung eines allgemeinen autonomen Reflexes, Arch. f. d. ges. Physiol. **197**:432, 1922.

10. Schilf, E., and Schuberth, A.: Ueber das sogenannte psychogalvanische Reflexphänomen beim Frosch und seine Beziehung zum vegetativen Nervensystem, Arch. f. d. ges. Physiol. **195**:75, 1922.

11. Richter, C. P.: The Significance of Changes in the Electrical Resistance of the Body During Sleep, Proc. Nat. Acad. Sc. **12**:214, 1926; Sleep Produced by Hypnotics Studied by the Electrical Skin Resistance Method, J. Pharmacol. & Exper. Therap. **42**:471, 1931; Pathologic Sleep and Similar Conditions Studied by the Electrical Skin Resistance Method, Arch. Neurol. & Psychiat. **21**:363 (Feb.) 1929.

12. Tower, S. S., and Richter, C. P.: Injury and Repair Within the Sympathetic Nervous System: I. The Preganglionic Neurons, Arch. Neurol. & Psychiat. **26**: 485 (Sept.) 1931; II. The Postganglionic Neurons, ibid. **28**:1139 (Nov.) 1932.

13. Schwartz, H. G.: Reflex Activity Within the Sympathetic Nervous System, Am. J. Physiol. **109**:593, 1934.

14. Landis, Carney: Psychiatry and the "Psychogalvanic Reflex," Psychiatric Quart. **6**:262, 1932; Psychology and the Psychogalvanic Reflex, Psychol. Rev. **37**:381, 1930.

EXPERIMENTS

Description of the Apparatus.—The apparatus (fig. 1) used in this laboratory was designed and assembled in the Electrical Laboratory of the Harvard Medical School, Department of Physiology, by Mr. E. L. Garceau. It is called a portable dermohmeter. The circuit used is the familiar voltmeter method of measuring resistance (fig. 2). Within the case is a 4.5 volt battery, which is turned on by the switch marked *Batt.* The battery is connected to the ends of a potentiometer marked *zero set.* The adjustable voltage from this potentiometer is led to a voltage divider which has three taps giving approximately 3, 0.3 and 0.03 volts. The low potential end of this voltage divider is led to a 0 to 30 direct current

Fig. 1.—The clinical dermohmeter which is described in the text. The case measures 11 by 8½ by 6½ inches (28 by 21 by 16 cm.).

micro-ammeter and thence to one electrode terminal. The other electrode terminal is connected with a key switch which selects one of three resistors of 100,000 ohms, 10,000 ohms and 1,000 ohms, respectively. The resistors or multipliers are connected, respectively, to the 3, 0.3 and 0.03 volt taps on the voltage divider. Thus, with no resistance between the electrode terminals at any position of the key switch the micro-ammeter will read full scale. When resistance is inserted between the terminals the readings of the micro-ammeter will be depressed. The micro-ammeter at all times indicates the amount of current flowing in the electrode circuit. The shunt around the micro-ammeter provides electromagnetic

damping on the meter needle and saves wear on the bearings and possible breakage of the needle and springs in transit. A small pole-changing switch is inserted next to the binding posts. A selector switch allows a choice of any two of the four outlets, which are connected usually to the palms and dorsa of the hands of the subject. A switch for cutting the subject out of the circuit is provided near the polarity switch. The readings of the meter in micro-amperes are converted into resistance in ohms by a table for each of the three ranges of the instrument.

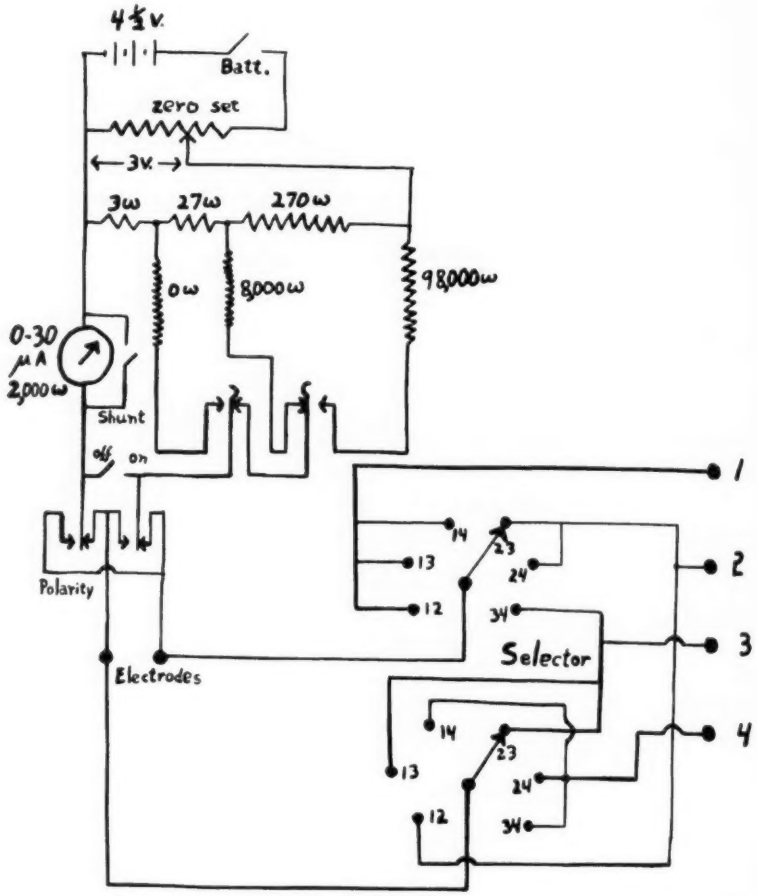

Fig. 2.—The electrical wiring of the clinical dermohmeter. In this figure *w* indicates ohms; *μA*, micro-amperes, and *v.*, volts.

The electrodes are circular disks of pure zinc having an area of 10 sq. cm. The electrode holders and zinc sulfate paste are similar to those described by Levine.[15] By means of the six possible combinations of the four outlets, the

15. Levine, Maurice: Measurement of Electrical Skin Resistance, Arch. Neurol. & Psychiat. **29**:829 (April) 1933.

resistance value of any one of them can be calculated according to the method of Richter.[16]

The apparatus here described has the advantage of being simple to operate and portable. It allows for *continuous* observation of the skin resistance and with reasonable care is "fool proof." It cannot be burned out when wrong connections are made. The current used is so minute that it is imperceptible to the patient, and there is no possibility that the resistance of the skin changes with the current. The price of the instrument probably more than compensates for the fact that it is not self-recording.

Use of Apparatus.—In order to avoid certain pitfalls into which many investigators working with the psychogalvanic reflex have fallen, the following precautions should be taken in using the method based on the electrical resistance of the skin.

1. The physical properties of the apparatus should be standardized as far as possible.[17] Many controversies have arisen in the literature regarding the psychogalvanic reflex because of essential differences in apparatus. It is known that the electrical resistance of the skin as measured depends on the electrical hook-up of the apparatus used and on the amperage and voltage of the current. If the Wheatstone bridge method for measuring resistance is used, the values of the individual resistances in the bridge must be given and held constant.[18] The electrodes should be nonpolarizing. Either the surface area of the part of the electrode in contact with the skin should be given, or the resistance should be expressed in terms of ohms per square centimeter of skin surface. The material from which the electrodes are made and the type of contact paste used should be stated.

2. The area of skin from which the current is led should be specified accurately. The physiologic differences between the palm and the dorsum of the hand must be carefully recognized[19] and kept distinct. Breaks in the skin or injury of the skin must be avoided under or near the electrodes.[20]

3. The conduct of the experiment must be such as to control as closely as possible all influences on the sympathetic nervous system other than the one under observation. It must be remembered that the resistance of the skin rises considerably during sleep and falls markedly under the stress of emotion. The room in which the experiment is conducted should be kept as quiet as possible and at a uniform, comfortable temperature. Needles or other disturbing apparatus should be kept from the sight of the patient. The changes in resistance due to altering the patient's position, sighing, coughing or laughing must be noted. Consideration should be taken of the time of day at which an experiment is made and any possible relationship to meals, fatigue or menstruation. In connection with experi-

16. Richter, C. P.: A Study of the Electrical Skin Resistance and the Psychogalvanic Reflex in a Case of Unilateral Sweating, Brain **50**:216, 1927.

17. Forbes, T. W., and Landis, Carney: A Systematic Investigation of Methodology in the Measurement of Electrical Phenomena of the Skin, Psychol. Bull. **29**:675, 1932.

18. James, H. E. O., and Thouless, R. H.: A Note on the Effect of Polarization in Psycho-Galvanic Experiments, Brit. J. Psychol. (Gen. Sect.) **17**:49, 1926.

19. Richter, C. P.: Physiological Factors Involved in the Electrical Resistance of the Skin, Am. J. Physiol. **88**:596, 1929.

20. Farmer, E., and Chambers, E. G.: Concerning the Use of the Psychogalvanic Reflex in Psychological Experiments, Brit. J. Psychol. (Gen. Sect.) **15**:237, 1924.

ments requiring the repeated measurement of the resistance of the skin over a period of days, it should be noted that there is considerable variability in the same subject from time to time, some of which is apparently not related to any of the factors mentioned. The weather and the patient's mood may be additional factors to be taken into account.

4. In evaluating results it must be remembered that even when the preceding factors are controlled a change in resistance may be due physiologically to activity in the sympathetic nerve centers, to activity elsewhere along the course of the sympathetic chain to the skin or to direct changes in the permeability of the cell membranes in the sweat glands of the skin directly under the electrode.

For the most part, the experiments reported here were performed in a small, quiet laboratory, with the patient either lying down or sitting in a comfortable

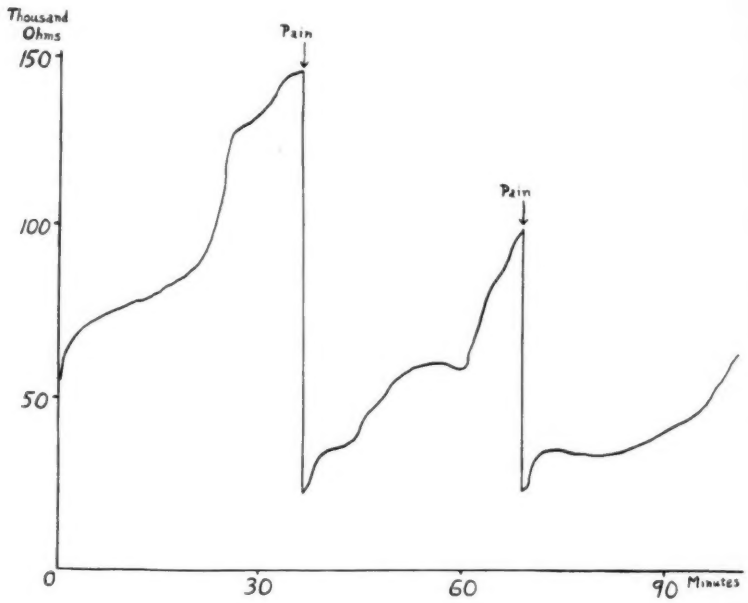

Fig. 3.—Graph of the electrical resistance of the palmar skin, showing the decrease in resistance caused by pain. (In figures 3 to 5 the curves have been smoothed for convenience in reading.)

chair. The electrode holders were adjusted so that the electrodes made contact with the palms and dorsa of the hands, as described by Levine.[15] Readings of the resistance were taken for from one-half to one hour as the patient relaxed and became accustomed to the situation. It was found that the dorsal resistance fell gradually and then became level, while the palmar resistance tended to rise somewhat. After a fairly steady base line was obtained the experiment was continued.

An example of the type of problem in which this method gives positive results is illustrated in figure 3. The effect of pain on the electrical resistance of the skin was observed. Readings were taken continuously for thirty-five minutes while the patient lay quietly in bed. The resistance gradually rose as the patient

grew accustomed to the apparatus. Pain was then produced by pricking the skin of the arm with a needle. This caused a marked drop in the resistance, indicating sympathetic stimulation. The resistance then rose gradually for the next thirty minutes. Then pain was produced again and caused another drop in the resistance. Results similar to these are obtained with great regularity whenever the sympathetic nerve supply to the skin under the electrodes is intact. In two patients in whom alcohol had been injected into the left stellate ganglia there was no change in the

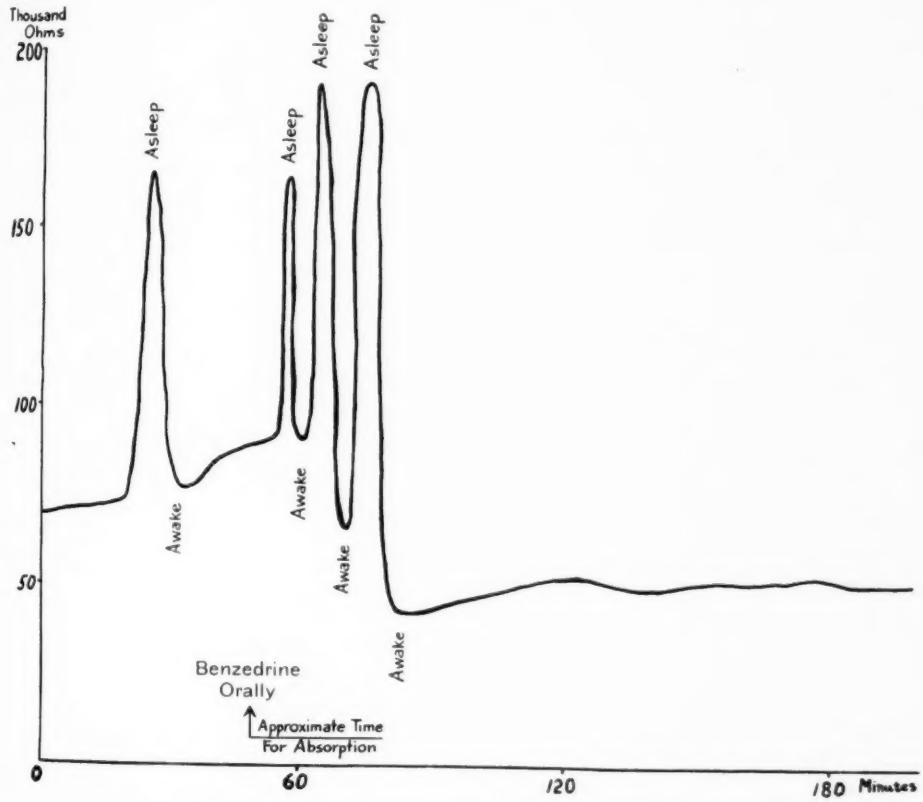

Fig. 4.—The electrical resistance of the palmar skin of a patient with narcolepsy. Four attacks of sleep occurred, and each was accompanied with a rise in the resistance. Following the administration of benzedrine, there were no further attacks, and the resistance maintained a low level.

resistance over the left palm on painful stimuli, but there was a marked response on the right.

Figure 4 represents the results of an experiment on a patient with narcolepsy. A new drug, benzedrine,[21] related to ephedrine was used to prevent

21. Printzmetal, M., and Bloomberg, W.: The Use of Benzedrine for the Treatment of Narcolepsy, J. A. M. A. **105**:2051 (Dec. 21) 1935.

the attacks of sleep. In the control period before the drug had been absorbed (from the beginning of the experiment to thirty minutes after the oral administration) the patient had four attacks of somnolence, each of which was accompanied by a marked rise in the electrical resistance of the skin, indicating sympathetic inhibition. Following the action of the drug there were no further attacks for the remaining two hours of the experiment, and the resistance continued at a low level. In control experiments, in which a solution of sodium chloride was used instead of the active drug, the attacks of sleep continued and were accompanied, as before, with large increases in the electrical resistance of the skin. These experiments corroborate the view that benzedrine is a stimulant of the sympathetic nerve centers.

Procedure in Experiments on Patients with Migraine.—The patients chosen for this work all gave a clearcut history of severe, incapacitating recurrent headaches superimposed on a background of normal health. In each case the headaches were usually accompanied by nausea and vomiting. Other features, such as hemicrania, visual scotomas and a hereditary history, were not constant. Each patient had been thoroughly studied medically and neurologically, but no organic disease had been revealed. The diagnosis of migraine in each case had been arrived at independently by each of a number of physicians. Doubtful cases were not included.

Experiments were performed on seven patients during the relief from the headache obtained by the intravenous or subcutaneous administration of ergotamine tartrate.[22] The dosage varied in individual cases. The smallest effective dose was 0.4 cc. of a 1:2,000 solution; the largest was 1 cc. of the same solution. The duration of the headache before the experiment was started varied from a few minutes to several hours. In one case the experiment was repeated on a second occasion. In another case the electrical resistance of the skin was measured during the spontaneous disappearance and reappearance of the headache. In another case ergotamine was given on a second occasion when no headache was present. In addition the same experiment was performed on four normal persons without headache.

RESULTS

There was no essential change in the electrical resistance of the skin in any of the experiments that could be correlated either with the action of the ergotamine or with the disappearance of the headache (fig. 5). In all the experiments the usual drop in the resistance (psychogalvanic reflex) caused by pinching the skin was present as definitely after the ergotamine had been administered as before. There was no change in the resistance during the spontaneous disappearance and reappearance of the headache in the one case in which this was observed. In one instance, while the resistance was being measured the patient (who was having severe headache on the left side) began to experience numbness and tingling in the right side of the mouth and on the lips. This gradually spread so as to involve the cheek, neck and right arm. After ten minutes the sensations disappeared in reverse order. The patient was

22. Ergotamine tartrate is prepared under the commercial name gynergen by the Sandoz Chemical Works, Inc.

a physician whose headaches were frequently associated with such a "march" of neurologic symptoms. During the entire sequence there was no change in the electrical resistance of the skin. In the patients without headache there was likewise no change in the resistance after the administration of ergotamine. The average level of the resistance in all the patients studied was within normal limits.

COMMENT

Admittedly this series of experiments is not large, but the uniformity of the results seems to make a larger series unnecessary. Conclusions regarding the sympathetic system in migraine obviously depend in these experiments on the validity of the electrical resistance of the skin as

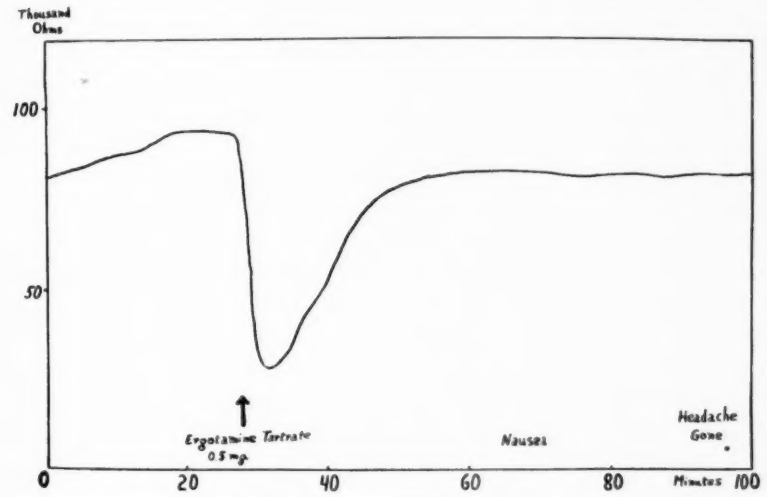

Fig. 5.—The electrical resistance of the palmar skin of a patient with migraine during the relief of the migraine headache produced by ergotamine. The drop in the resistance caused by the pain of the injection is shown. There was no change in the resistance during the relief of the headache.

an indicator of sympathetic activity. This question has already been discussed. Stimulation of the isolated sympathetic chain in animals and all clinical conditions in man known to be associated with activity of the sympathetic system (viz., pain, sweating, vasomotor changes and sleep) are accompanied with definite changes in the electrical resistance of the skin. Since many different factors may operate through the sympathetic system to produce a change in the resistance, when such a change occurs an experiment must be well controlled in order to warrant the drawing of any conclusions. But the situation is decidedly more favorable in the absence of a change in the resistance. It is difficult to see

how any change of importance in the general activity of the sympathetic system could occur without immediately being reflected in a change in the electrical resistance of the skin.

It is possible that a local change in the activity of the sympathetic nerves supplying the intracranial contents could occur without a concomitant change in the activity of the sympathetic nerves to the palms. The experiments reported here offer no evidence bearing on this point. To my knowledge there is no physiologic reason for believing that such isolated activity can take place in the sympathetic nervous system. But if local sympathetic activity did enter into the mechanism of the attack of migraine, one would still be justified in saying that the emphasis in further work should be along the lines of possible causes for such local activity and away from the prevalent theories of general sympathetic dysfunction.

SUMMARY

The need is pointed out for an accurate means of continuously measuring the activity of the sympathetic nervous system in the study of migraine. The method of utilizing the electrical resistance of the skin is presented for the purpose. The physiologic status of the electrical resistance of the skin is briefly summarized, and the literature dealing with the use of this method in problems involving the sympathetic nervous system is reviewed. A simple portable apparatus for the continuous measurement of the electrical resistance of the skin is described, and criteria are set down for its proper use. Illustrations are given of experiments in which positive results were obtained paralleling changes in the sympathetic activity.

In seven patients with migraine the electrical resistance of the skin was measured continuously during the period of relief from a characteristic headache obtained by the use of ergotamine. There was no significant change in any instance, indicating that the relief from the headache was not accompanied with a change in the activity of the sympathetic nervous system as a whole. In one case a similar lack of change was observed during the spontaneous disappearance and reappearance of the headache. In another a "march" of neurologic symptoms during a typical headache was likewise unaccompanied with any change in the electrical resistance of the skin. In four control patients without headache ergotamine caused no change in the electrical resistance of the skin.

CONCLUSION

The result of the present investigation indicates that migraine is not a disease caused by general sympathetic dysfunction.

CALVARIAL HYPEROSTOSIS AND THE ACCOMPANYING SYMPTOM COMPLEX

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Reexamination of roentgenograms of 6,650 human skulls accumulated over a period of twenty-four years disclosed four types of thickening of the calvaria, named in order of their definiteness: hyperostosis frontalis interna, nebula frontalis, hyperostosis calvariae diffusa and hyperostosis frontoparietalis. The type of thickening which is most characteristic and which led to the study involves the frontal bone, which has on its inner table deposits of new bone with occasional extensions to other bones in the base of the skull. This overgrowth or deposit of cancellous bone lies on the inner table and is covered on its intracranial aspect by a smooth lamella of compact bone. There is no evidence of an inflammatory process. This deposit of bone is increased in density, as seen in roentgenograms. Increase of density progresses from the inner table outwardly through the diploe. The hyperostotic deposit is progressive, and roentgenographically it can be divided into degrees of development. Morphologically, it may be either nodular or sessile. In certain cases the orbital plate of the frontal bone is chiefly, if not exclusively, involved. This change may be combined with calcification in the falx cerebri.

The second type of calvarial change consists of a triangular or ellipsoid area of increased density located in the squama frontalis, extending downward from a base on the sagittal plane. There are no projections from its intracranial surface, and it is less clearly defined than the preceding type of hyperostosis. It also has a progressive development.

The third type of hyperostosis is one in which there is a generalized increase in thickness of the entire vault, with an increase of density of the diploe which is in excess of that to be anticipated from mere increased volume of bone.

The fourth type, which is perhaps but a step in the development of the third, has the maximum thickening of the diploe at approximately the central point of the parietal and squamous portions of the frontal bones. This type of hyperostosis produces a gentle grooving of the vault at the site of the sagittal and coronal sutures.

Read at the Sixty-First Annual Meeting of the American Neurological Association, Montreal, Canada, June 3, 1935.

In this connection it may be pointed out that some evidence was found to give reasonable grounds for believing that there may be a process the antithesis of overgrowth of bone, namely, regional thinning of the vault of the skull.

In all of the hyperostoses there is bilateral symmetry, both in extent and in degree, of the osseous changes. There is no change in the outer table of the skull, which remains regular and smooth. A noteworthy point is that the skull does not increase in size. This fact is significant for the reason that the increased volume of the bone under these circumstances has to be accommodated at the expense of the capacity of the cranial cavity.

The incidence of the several types of hyperostosis in the 6,650 skulls studied was as follows:

Hyperostosis frontalis interna	1.44%
Nebula frontalis	1.14%
Hyperostosis calvariae diffusa	0.6%
Hyperostosis frontoparietalis	0.3%

The incidence of all types was 3.5 per cent in 6,650 skulls. In a general hospital in a period of twenty-four years the incidence was 0.05 per cent.

Hyperostosis frontalis interna has long been observed at autopsy and among specimens in museums. I have been unable to find a description of the other three types of thickening of the calvaria. In repeated search of the literature only 3 cases of hyperostosis frontalis interna described during the patient's life were found.[1] Each of the 3 patients had a psychosis.

The hyperostoses are of two orders. In one, bone is deposited on the inner table, chiefly on that of the frontal bone though it is found rarely on that of the squama temporalis. In 1 case there was a hyperostosis which projected intracranially from the parietal bone at the vertex. There is serious doubt whether this kind of thickening belongs to the same type as hyperostosis frontalis interna. The other division comprises the remaining three types of hyperostosis and is distinguished by the fact that the process is confined to the diploe and neither table is altered.

The roentgenograms demonstrated that there were one certain and three additional, but less certain, groups of changes in the skull. In

1. Morel, Ferdinand: L'hyperostose frontale interne. Syndrome de l'hyperostose frontale interne avec adipose et troubles cérébraux, Paris, Gaston Doin & Cie, 1930. Van Bogaert, Ludo: Le syndrome de l'hyperostose frontale interne chez une malade présentant par ailleurs une cécité psychique par hémianopsie double, J. de Neurol. et de psychiat. **30**:502, 1930. Schiff, P., and Trelles, J. O.: Syndrome de Stewart-Morel (Hyperostose frontale interne avec adipose et troubles mentaux) d'origine traumatique, Encéphale **26**:768, 1931.

order to determine whether these roentgen entities were important, cases in which histories were available were analyzed. The clinical analysis determined that there is a symptom complex accompanying the osseous changes which is as characteristic as the roentgen findings. The symptom complexes of the several types are closely allied and in the future they may be proved to be identical.

In the search for material to extend the roentgen findings and the clinical analysis, the St. Louis City Sanitarium offered a promising field as a source of cases. Thirty-six cases in which the stigmas of the disorder occurred were selected. In 14 of these in which a specific psychiatric diagnosis of unclassified dementia had not been established a roentgen examination of the skull was made. In 7 the changes in the skull characteristic of calvarial hyperostosis were found and the incidence according to type was 5 cases of hyperostosis frontalis interna, 1 case of nebula frontalis and 1 of hyperostosis calvariae diffusa.

In order to corroborate the roentgen findings, permission was obtained from Prof. Robert J. Terry, of the department of anatomy, to examine his invaluable osteologic collection. Among 582 skulls suitable for examination 46 examples of the several types of hyperostosis were found, as follows:

Hyperostosis frontalis interna	29 cases
Nebula frontalis	14 cases
Hyperostosis calvariae diffusa	3 cases

The fact concerning the persons in whom the changes in the skull were found were meager, as the skeletons were from unclaimed bodies. However, this material amply confirmed the morphologic aspects of the roentgen examinations of the skull, and, further, it indicated that the different types of hyperostosis coexist and perhaps blend into each other. In almost all the pathologic cases there was a degree of thickening of the remainder of the vault of the skull.

The fact that the hyperostoses coexist in the same persons and that the skulls are generally thickened in cases of all types sustains the view that, though morphologically distinct, all types have the same fundamental etiology; this is indicated also by the closely related clinical phenomena.

SYMPTOMATOLOGY

The symptoms described in the case histories are a combination, more or less constant, of the following disorders: headache, often disabling and in patients with hyperostosis frontalis interna frequently referred to the forehead with occasional tenderness and a feeling of pressure; obesity or a tendency to obesity, which may be extreme and is of the rhizomelic type; muscular weakness and easy fatigue;

"nervousness"; a tendency to worry and depression; dimness of vision and occasional diplopia; epileptiform seizures; mental slowness in the lesser grades of involvement and dementia in those of full development; dizziness; disturbance of equilibrium and gait. Weakness of the seventh nerve is also frequently noted; occasionally there is difficulty in speech, which is apparently motor; in a case observed recently there was loss of the sense of smell; neuralgia of the fifth nerve has not been observed; there may be dragging of a lower

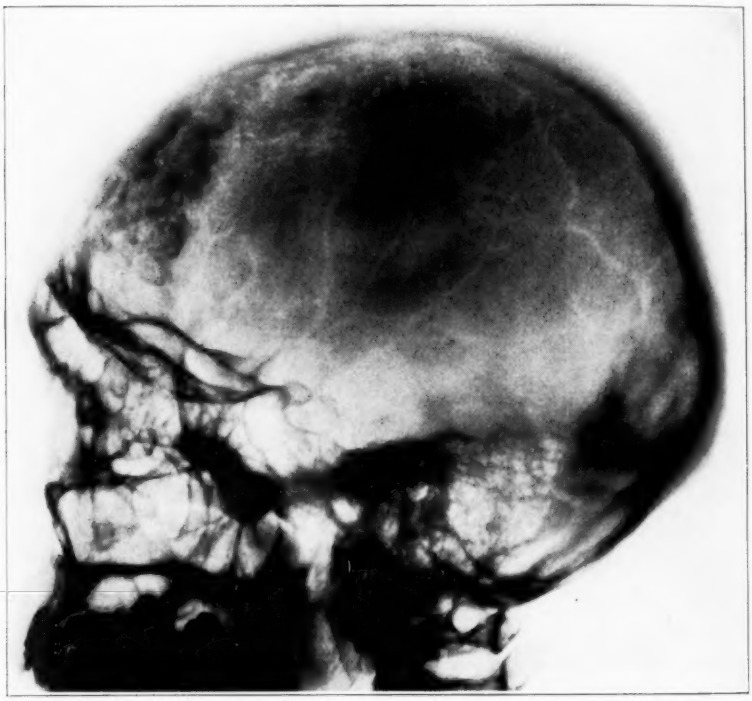

Fig. 1.—Roentgenogram of the skull in the lateral position. An extreme example of hyperostosis frontalis interna.

extremity or weakness of any extremity, and there is a general neuromuscular insufficiency; there is overgrowth of hair on the chin and less frequently on the upper lip in female patients. Ninety-eight per cent of the cases have occurred in women. There is no evidence of racial selection.

Thyroid disorder was associated in 4.4 per cent of the cases, and there were two cases of clearcut acromegaly among the patients with hyperostosis calvariae diffusa.

The symptom complex and the roentgen evidence are so characteristic that when the one is observed the appearance of the other

may be foretold in a substantial proportion of the cases. In all probability the symptoms antedate the osseous changes for the reason that the latter require much time for their development. The disorder is one of slow development and progress. In its incipiency, therefore, its existence would be difficult to determine.

The differential diagnosis of the disorder has to be made first from osseous dystrophies which have overgrowth as a feature. The condition cannot be fitted into any of the osseous dystrophies which are now known. The osseous change is confined to the skull, and no

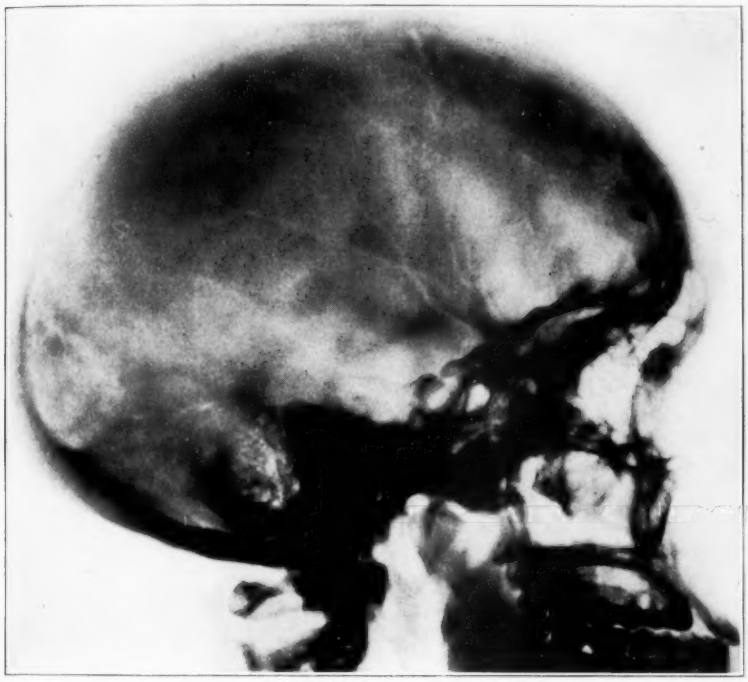

Fig. 2.—Hyperostosis frontalis interna in a 32 year old patient. Obesity and depression were practically the only symptoms.

evidence has been found that the remainder of the skeleton is involved, though a systematic search in this direction has not been made. Such search as has been made on patients and on anatomic material indicates that the change is limited to the skull. It was found on examining the roentgenograms in 27 cases of acromegaly that the hypertrophy or overgrowth of bone in that disease was readily distinguished from the changes of the hyperostoses. The unequal incidence in the two sexes separates these conditions from other osseous dystrophies, practically all of which occur with approximately the same frequency in the two sexes.

Likewise clinically, the symptom complex present in cases of the hyperostoses cannot be brought into relationship with the disorders which have an equal or nearly equal distribution in the two sexes. Moreover, the condition is one of rather late adult life, the youngest patient observed being 18 years of age. The disorder at present cannot be considered as part of any of the endocrine diseases as such diseases are at present known. Certain of them, as has been pointed out, can coexist with the hyperostoses.

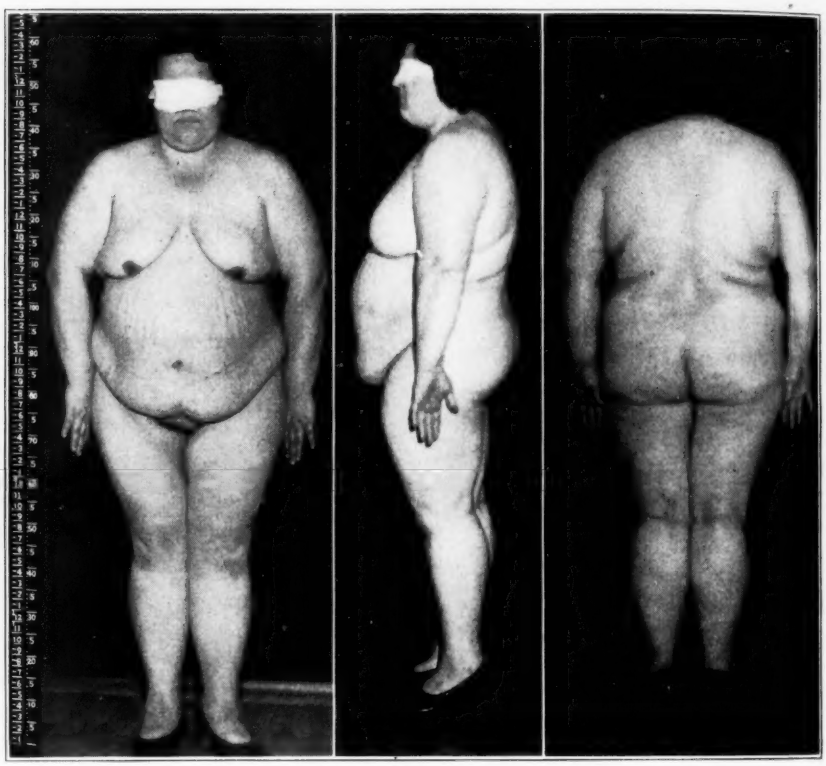

Fig. 3.—Photographs of the patient the roentgenogram of whose skull is shown in figure 2.

The evidence is that the condition is a metabolic disease in which, as far as is known at present, fat and calcium metabolism only are at fault. However, it may be that these substances are assimilated beyond the capacity of the subject to dispose of them. The fact that an overwhelming proportion of the cases occur in women seems to indicate that the disorder bears a relationship to the function of reproduction. However, only about 50 per cent of the patients had borne children, and many of them were single Too much emphasis cannot

be laid on this point, for there is the additional fact that the condition occurs, rarely to be sure, in the male.

The patients sooner or later come under the observation of the neurologist or neurologic surgeon. In the past the manifestations have generally been classified as neurotic, psychoneurotic, hysterical, indicative of tumor of the brain, and so forth, though none of these designations is suitable. Unquestionably the psychic manifestations, if progressive, terminate in dementia. The patients with less fully developed psychic manifestations appear to be doomed to chronic invalidism.

THERAPY

Certain therapeutic suggestions have been derived from this study and are offered. In cases of hyperostosis frontalis interna, if there is disabling headache or major manifestations suggesting cerebral involvement, for example convulsions, it appears that much good might be accomplished by turning down a frontal bone flap. This in any case should both terminate the headache and arrest the progress of the hyperostosis. It is possible that failure of vision might be helped by decompression of the optic nerves, though it must be stated that in all cases in which nervous symptoms have been present evidence of organic disease or focal signs have been lacking.

It is useless to administer antisyphilitic treatment in the belief that the disorder is cerebrospinal syphilis. The administration of thyroid on the theory that thyroid insufficiency is a part of the disease seems out of place in these cases unless hypothyroidism is a known complication of the disorder. The most valuable therapeutic suggestion related to the condition is that those who treat patients with this malady avoid the error of treating them for something which they do not have.

SUMMARY

Certain roentgenographic changes in the skull and their incidence are described. These findings have been corroborated with a study of dry anatomic material. A symptom complex which is found in patients showing changes in the skull is described. The differentiation of this symptom complex and the changes in the skull from other disorders is made. The importance of the condition is emphasized. Certain speculations as to etiology and therapeutic suggestions are advanced.

NEUROPSYCHIATRIC SYNDROMES ASSOCIATED WITH HYPEROSTOSIS FRONTALIS INTERNA

PRELIMINARY REPORT

ARCHIE D. CARR, M.D.
ST. LOUIS

Ferdinand Morel [1] in 1930 called attention to a group of symptoms associated with hyperostosis of the internal tables of the frontal bones. Sherwood Moore has delimited what seems to be a definite symptom complex associated with changes in the frontal bones of the skull. In the past eight months it has been possible to follow rather closely 17 cases of varying degrees of hyperostosis of the internal tables of the frontal bones and to concur in Moore's opinion that there is apparently a symptom complex or syndrome associated with these changes in the bones of the skull.

The group of symptoms and signs found, namely, headache, visual disturbance, dizziness, defects of memory, convulsions, weakness and easy fatigability, with various types of mental changes, are extremely general and may occur in numerous neurologic states. A significant finding is that these symptoms coincident with the changes in the frontal bones were found almost exclusively in females; 98 per cent of Moore's series of 229 patients and all of my 17 patients were women.

The importance of the recognition of hyperostosis of the frontal bones of the skull lies in the fact that it assists in more accurately classifying cases of this condition, in many of which the changes in the frontal bones have masqueraded as tumor of the brain or as reactions associated with chronic invalidism. A number of the patients observed have been referred in the first instance to a neurologic surgeon. Some have been subjected to exploratory operations, which have resulted in negative findings. This has been particularly true of patients with convulsive manifestations occurring at the age at which symptoms and signs of the condition appear, namely, from 35 to 40 years.

The changes in the frontal bones of the skull could not possibly account for the composite picture or the pictures presented by individual patients. These changes must be considered purely as roentgenologic evidence of an entity which is probably metabolic in origin. In support

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Read at the Sixty-First Annual Meeting of the American Neurological Association, Montreal, Canada, June 3, 1935.

1. Morel, Ferdinand: L'hyperostose frontale interne, Paris, Gaston Doin & Cie, 1930.

of such a theory is the high frequency of obesity, which occurred in 64.7 per cent of the patients in my series. Morel's case occurred in an obese psychotic woman, and Moore has found obesity in about one half of his patients with hyperostosis. With the obesity, a number of patients have exhibited a marked increase in dextrose tolerance. Basal metabolic rates have not been estimated in enough cases to warrant any conclusions. There is indication, however, that the rates tend to be low.

Menstrual disturbances of various kinds occurred in 13 of my 17 patients. Usually these patients complained of profuse painful menstruation and also of frequently passing clots. Irregularity in the menstrual cycle occurred in a few. Practically all these patients had gynecological consultations, and the results of examinations were entirely negative. In fact, several of these patients were referred by gynecologists after having received various types of endocrine therapy without improvement.

The striking symptoms consisted of headache, difficulties of memory, weakness and easy fatigability, dizziness, visual disturbances and convulsive seizures. The incidence of symptoms was as follows: headache, 82.3 per cent; memory defects, 88.2 per cent; menstrual disturbances, 76.4 per cent; dizziness, 64.7 per cent; mental changes, 58.8 per cent; weakness, 58.8 per cent; visual disturbances, 41.1 per cent; convulsive manifestations, 35.3 per cent; muscular defects, 17.5 per cent, and hypertension, 11.7 per cent.

Each of the patients has been studied on numerous occasions. There has been some fluctuation in symptomatology, but headache, weakness, dizziness and defective memory were consistent complaints.

The psychiatric changes observed in this group varied widely, but they were predominantly a confusional state of greater or less duration with marked irritability and memory defects. This is at variance with the manifestations exhibited by Morel's patient, who apparently showed evidence of deterioration, but that patient was much older than the patients in Moore's and in my series. Likewise in Moore's patients with hyperostosis, who were inmates of the St. Louis Sanitarium, the condition masqueraded as senile dementia.

An attempt has been made to treat a group of these patients with amino-acetic acid by feeding large quantities of gelatin daily. This has been continued because of the favorable results which have followed. Amino-acetic acid therapy was originally used in an attempt to relieve the marked weakness complained of by one of my patients. The change in the entire picture was so striking that the use of amino-acetic acid has been continued. Several patients have been studied from the point of view of creatine-creatinine metabolism. These patients showed creatinuria, which disappeared under therapy with amino-acetic acid.

Several typical case histories may assist in demonstrating the picture.

REPORT OF CASES

CASE 1.—F. L. M., a woman aged 62, entered the Barnes Hospital in September 1934. She complained of severe headaches of one year's duration and exhibited an uncertain, unstable gait. She was extremely garrulous and recounted in great detail the various phases of her history. The headaches occurred daily and frequently aroused her from sleep. She also had severe pain in the neck. During the few weeks before admission her gait had been very uncertain and she had been extremely weak. She had experienced difficulty in remembering names and small duties. She remembered being in a railroad station on her way from Denver but did not remember her trip or under what circumstances she arrived in the Barnes Hospital. This tendency to confusion was observed from time to time during the course of her stay in St. Louis.

Physical Examination.—The patient was 5 feet, 1 inch tall (1.5 meter) and weighed 120 pounds (54.4 Kg.). She had lost 25 pounds (11.3 Kg.) in the past few months. The skin was wrinkled and dry. There was increase of hair on the upper lip. Lateral nystagmus was present in both directions. There were marked swaying in the Romberg position and a staggering gait, with dragging of the left foot. The deep reflexes were everywhere hyperactive, but no pathologic reflexes were found. Roentgenologic studies of the skull showed marked thickening of the internal tables of the frontal bone (nebula frontalis). Under treatment with gelatin the patient made a surprising readjustment; the headache and weakness disappeared and she gained weight. She was able to manage a simple apartment by herself and after four months to return to her own home in California, where she has continued well.

CASE 2.—R. C., a woman aged 28, was seen early in February 1935. She complained of attacks in which she saw only the left half of an object. The attacks lasted from thirty minutes to one hour and were followed by severe frontal headache on the left side and aching of the left side of the face. The tongue seemed to become big. Memory was poor. Energy was good, and the patient did not tire readily. When she suffered from headache she tended to become confused. Menstrual periods started at 16 years and had always been irregular. The flow was copious and lasted five or six days. Activity had to be limited during the menstrual periods.

Examination.—The patient was 5 feet, 3 inches (1.6 meter) tall and weighed 138 pounds (62.6 Kg.); physical and neurologic examination gave entirely normal results. The visual apparatus was normal in all respects. Gynecological examination revealed a normal pelvis. Roentgenologic studies of the skull showed hyperostosis frontalis interna.

Course.—At the time of writing this patient has been consistently under therapy since February 5. Before that date attacks had occurred on an average of once every two weeks; she has suffered one attack of headache not associated with visual disturbance since starting treatment. The menstrual cycle has likewise shown a change, being now of the twenty-eight day type, with periods lasting two days.

CASE 3.—C. E. H., a woman aged 38, has been under observation since May 1932. She was referred because of three major convulsions in the preceding six months. Aside from these attacks she had been well, though she was always tense and socially active.

Examination.—The pupils were irregular and rather sluggish, but no other disturbances referable to the cranial nerves were present. The knee and ankle jerks were active and greater on the left than on the right side. There was a Babinski sign on the left. Otherwise examination gave negative results.

The height was 5 feet, 3 inches (1.6 meter); the weight, 126 pounds (57.2 Kg.). Serologic examination, including examination of spinal fluid obtained by lumbar puncture, gave negative results. Stereoscopic roentgenograms of the skull showed the condition now known as hyperostosis frontalis interna; at the time this was thought to be evidence of an endothelioma.

Course.—The patient has reacted well to therapy with phenobarbital. At the time of writing the findings remained the same, except for some progress in the changes in the skull. The patient was not given amino-acetic acid.

COMMENT

It is not clear how treatment with amino-acetic acid has affected these patients, but while receiving this therapy some have shown astonishing results. It is, of course, necessary to follow a much larger series of patients with carefully controlled metabolic conditions before definite conclusions can be drawn.

DISCUSSION

On Papers of Dr. Moore and Dr. Carr

Dr. Sidney I. Schwab, St. Louis: I wish to point out that roentgen studies of patients with the type of condition described give much more certain and positive evidence than the clinical description. Dr. Carr has been able to sketch the possible clinical picture associated with these well defined roentgen pictures. I am sure all are impressed with the fact that in Dr. Carr's presentation the clinical sketches were meant to be only temporary. My own experience with cases of this type goes back somewhat less than a year, to the time when Dr. Sherwood Moore called my attention to a curious appearance in the skull of a patient whose case he was assisting me in interpreting—rather he was interpreting the skull, and I was listening to his interpretation. He was at that time much impressed with the positive features of the roentgen appearances in these cases, and in that particular case the clinical type corresponded well with the type that has been sketched by Dr. Carr. Since, I have seen perhaps 5 or 6 cases in which the diagnosis as based on the roentgenograms seemed to be certain. In 1 case hemianopia has developed. This case was that of an unmarried woman, aged 34. I saw her when she was about 8 years of age, and I have a clinical record of her condition, as well as a roentgenogram of her skull made at that time. When compared, the two sets of roentgenograms show no great similarity. The hemianopia was evidently of recent occurrence. The patient had attacks that were interpreted as minor epileptic seizures. She was defective in intellectual development and had complained of a great amount of fatigue. This case evidently belongs to the class under discussion, and when I say that this patient was subjected to a ventricular study with injection of air on the supposition that she might have a cerebral neoplasm, this fortifies the statement made by Dr. Carr that the recognition of the condition clinically will save or should save patients from diagnostic surgical intervention on the basis of suspected neoplasm. I think it is fortunate that the two papers read are to be submitted here for critical discussion. From my own past experiences I am certain that the critical attitude of this society will be

demonstrated. I do not know whether this is an important contribution to American neurology from the midwestern city of St. Louis or not: I hope it will turn out to be, but it is an extremely interesting and perhaps an important step in advancing the knowledge of an obscure clinical condition.

DR. MORTIMER: The problem of changes in cranial structure and form is one on which I have been working for several years, and there are certain facts to which I wish to call attention. Toward the end of the last century a certain amount of attention was given to this question by pathologists who examined autopsy material in hospitals for patients with mental disease in England. In 1898 Beadles, in the *Edinburgh Medical Journal,* reported the occurrence of calvarial thickening in psychotic patients. In his own postmortem material, taking the normal calvarial thickness as varying from ⅛ to ¼ inch (0.32 to 0.64 cm.), he found increase in thickness in 21 per cent of his series, which numbered 234 cases. He also quoted three other authors, who together reported on over 2,000 autopsies in cases of mental disease and found that the incidence of hyperostosis of the calvarium varied from 17 to 77 per cent. Beadles found that the condition occurred twice as frequently in females as in males. He noted that the condition might affect the whole calvarium, that often the frontal bone was most affected and that in certain cases there was a diffuse deposit of bone on the inner table in that region.

I came to recognize this condition in the cranial roentgenogram in a case of dementia praecox, that of a man aged 26, a patient in the Worcester State Hospital, who showed other evidence of dyspituitarism. It was this which led me to a study of the cranial changes in cases of acromegaly and other pituitary disabilities and ultimately to the experimental investigation of the effects of hormones from the anterior lobe of the pituitary gland on cranial form and structure.

The first investigation, in 1933, carried on together with Leveen and Rowe, was based on the study of roentgenograms of the craniums of 3,000 patients specially referred for endocrine study to the Evans Memorial Hospital. This, it should be noted, constitutes a specially selected population. We found abnormal craniums in 17 per cent of the cases, and subsequently it was found that in 56.9 per cent of the 17 per cent of cases a diagnosis of pituitary disorder had been arrived at independently.

Dr. Moore said, I think, that he found hyperostosis in 3.5 per cent of 6,650 skulls. The cases occurred, I presume, in a general hospital population, and I think that the higher incidence of 17 per cent in our study may be due to the fact that in the population of the Evans Memorial Hospital the occurrence of pituitary disabilities is much higher than that which would be found in the population of any general hospital.

In our dysplastic group we found that in a further 14.2 per cent of the cases the condition was associated with lesions of the central nervous system; an additional point of interest was that in 12.7 per cent of the whole dysplasic group the condition had been diagnosed by other physicians, at one time or another, as psychotic or psychoneurotic, while 5.6 per cent of the cases occurred in children presenting either mental deficiency or problems of behavior.

In the lateral roentgenogram of a woman, aged 42, who weighed 300 pounds (136 Kg.) and was suspected of having a pituitary tumor, there seemed to be some evidence of erosion of the base of the stella turcica. There was a marked, generalized hyperostosis of the calvarium, but there were also other changes to which I wish to draw particular attention—changes which, I believe, could be

noted in some of the material that has just been demonstrated. In this woman the frontal sinus was much larger than normal in the female; the same was true of the maxillary antrums and the sphenoid sinus. The face was hyperpneumatized, and there was a definite degree of prognathism.

These changes were due to a period of hyperpituitarism in youth, and the subsequent sclerosis of the previously expanded calvarium occurred in later years, with functional involution of the pituitary. This type of change is what we have called cranial dysplasia of type II.

Another patient presented an example of cranial dysplasia of type IV, a condition which we recognize as being due to consistent hypopituitarism, occurring especially in patients showing adiposity and hypogenitalism. The patient was 18 years of age, and at one time weighed close to 600 pounds (272 Kg.). The head was small, and the face was small in proportion to the head. There was generalized sclerosis of the calvarium, the normal architecture of which was no longer seen. This, however, was most marked in the frontal region, on the inner table of which there was well marked formation of exostoses. There was hyperpneumatization of the face; the frontal sinus had reached the degree of development seen in a girl aged 10 or 12; the maxillary antrums were small, and the body of the sphenoid bone was poorly pneumatized. This gave definite evidence of faulty differential growth during the early part of the second decade, a sign of hypopituitarism. The face was decalcified, while the sclerotic change seemed to be confined to bone formed by the cranial endosteum.

In our series we found that those two types (type II and type IV) occurred ten times more frequently in female than in male patients, and it should be stressed that calvarial sclerosis is a characteristic component of both types.

Regarding the lateral roentgenogram of a patient whose case was first reported by Cunningham, in 1879, who had a large subarachnoid cyst of the parietal lobe of the brain and died of diabetes, I wish to emphasize that the calvarial changes under discussion today have been noted by others in the past. Thomson gave a detailed description of the calvarial changes—the great increase of calvarial thickness and density—so well seen in the roentgenogram. He also drew attention to the hyperpneumatization of the face. This is also a dysplasia of type II with early hyperpituitarism followed by sclerosis during the period of glandular hypofunction.

Another example of type II, which is also well known in the literature, is the case of Mr. Van W., reported by Cushing in the "Monographs of the Rockefeller Institute" in 1927. In that case the hyperostosis was so marked that the skull cap when dried weighed close to 500 Gm. This was due to an eosinophilic tumor of the pituitary gland.

In the production of changes in the calvarium, of which sclerosis or hyperostosis is a characteristic part, there is obviously a metabolic disturbance—a disturbance of calcium metabolism and, frequently, also an associated disturbance of fat metabolism. That the anterior lobe of the hypophysis is implicated is becoming gradually evident both from the changes known to occur in cases of lesions of the gland in man and from the results derived from experimentation with animals.

This morning I showed cranial roentgenograms of two rats, one of which, both before and after undergoing hypophysectomy, had been treated with a ketogenic fraction from the anterior lobe of the pituitary gland to the point at which the treated animal had become resistant, so that there was marked diminution in ketone output in the urine even when a potent ketogenic fraction was injected. Not only did the treated animal become fat (it weighed 353 Gm. while the control's weight was 163 Gm.), but its calvarium was markedly sclerosed. It is found that

before occurrence of the refractory state the animal does show true overgrowth or hyperpituitarism. When the refractory state is reached there occurs an inability to metabolize fat adequately, and at the same time there is an increased storage of calcium in the bones. I am inclined to believe that it is something of this sort which produces the hyperostosis and adiposity in the cases under discussion.

With reference to the greater frequency of the condition in the female, it may seem superfluous to point out that, compared with the male, the female shows hypopituitarism. In cranial size, especially as regards the facial component, as in stature, the female is smaller than the male. Also as far as metabolism is concerned she has a well marked tendency to handle fat and carbohydrate less efficiently than the male. One of woman's great problems is the tendency she has to become obese at a relatively early age. This is not a matter of diet alone. It is more likely, it is almost certain, that she has a sexual difference in glandular function of the nature of hypopituitarism as compared with the function in man. This affects not only growth but also the metabolism of carbohydrates and fats, especially when the period of active growth is over.

This is a constitutional disability in its widest sense, and it may be accentuated in races or families or in individual subjects, varying considerably in degree. It may be an inherited character or an endocrine disability arising in the lifetime of the individual subject, but in both cases the mechanism of its production is in all likelihood the same.

Finally, as to the symptomatology of these conditions, it may be said that at present from the anterior portion of the hypophysis alone can be separated seven active hormone fractions which exert profound physiologic effects on growth, on sex, on the thyroid and on the functions of the adrenal cortex. The hypophysis plays a dominant rôle in the metabolism of proteins, carbohydrates, fats, water and calcium. The possibility thus arises that disturbance of its function may give rise to a great number of constitutional or metabolic changes showing great variability in the resultant symptom complexes which different patients may show. A certain number of those are already well known to clinicians. Others are gradually being recognized. It should be borne in mind, however, that one such syndrome may in certain of its features bear a resemblance to others, there being certain components common to several symptom complexes.

The symptoms the patient presents will thus depend largely on the particular way the pituitary disturbance affects the general physiologic constitution of the subject. Thus, I have seen calvarial change in patients whose chief complaint was overgrowth for age, obesity, delayed maturity, premature senility or diabetes insipidus, and, as I showed this morning, in cases of lesion of the central nervous system as well as in cases of a clearcut Fröhlich syndrome and in cases of long-standing acromegaly.

On the other hand, the general symptoms may be vague and indefinite, such as loss of energy and vitality for no apparent reason, as if the patient merely suffered from an intensification of that slowing up of vital processes that normally comes with advancing years. After all, the process of growing old is largely the reverse of the process of growing up. In both of these processes the level of pituitary function is a dominant factor, and from the work that I have done in this field I have formed the opinion that the two types of cranial dysplasia which are characterized by either local or general calvarial hyperostosis have as their etiologic background a condition of hypopituitarism.

DR. WALTER TIMME, New York: Apart from the malformations of the skull, the symptoms in these cases are based on the low utilization of calcium, just as the symptoms in some cases are based on the low utilization of fats. The symptoms based on the low utilization of calcium depend on the necessity for a certain level of calcium in the blood stream and in the tissues for the normal neuromuscular stimulation and reactivity. This low utilization of calcium results in a spastic hyperactive state of the neuromusclar system, which reacts abnormally to external stimuli under such conditions of low utilization of calcium. The patients have myotatic irritability, myo-edema and spasms. They belong to a spasmophilic group. They have convulsions, often diagnosed as petit mal or even as epilepsy. The whole situation resolves itself symptomatically, if the patients are treated properly, on the basis of utilization of calcium.

ENCEPHALOGRAPHY

A REVIEW OF EIGHT HUNDRED ENCEPHALOGRAMS WITH SPECIAL REFERENCE TO SUBDURAL AIR

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AND
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Since its inception in 1919 [1] encephalography has become increasingly popular as a method of psychiatric diagnosis and research. The presence of pathologic changes too subtle for postmortem demonstration has been assumed on the basis of abnormal encephalographic findings alone.[2] For this reason, organic changes are diagnosed in cases of psychiatric conditions which heretofore have always been considered to be functional disorders.

Jacobi and Winkler [3] were unable to find a single normal encephalogram in 19 cases of chronic schizophrenia. Moore, Nathan, Elliott and Laubach [2] obtained encephalograms of 60 patients with schizophrenia, and although their patients were selected so as to eliminate known organic factors and although 10 gave no evidence of deterioration, none of the encephalograms showed a normal pattern. The same workers [4] examined 38 patients with manic-depressive psychosis and again were unable to find a single normal encephalogram. It seems unusual that organic changes were found so consistently in patients with supposedly functional psychoses.

In cases of epilepsy one would be more inclined to accept evidence of occasional pathologic changes, even in cases of so-called idiopathic epilepsy. Fay,[5] however, stated that every one of the 59 patients examined by him showed characteristic encephalographic abnormalities.

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* Commonwealth Fund Fellow at the Colorado Psychopathic Hospital.

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3. Jacobi, W., and Winkler, H.: Encephalographische Studien an chronisch Schizophrenen, Arch. f. Psychiat. **81**:299, 1927.

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Notkin [6] found encephalographic evidence of a pathologic condition in 9 of 17 cases of idiopathic epilepsy.

That abnormal encephalograms are found in the majority of cases of dementia paralytica has been demonstrated by Ebaugh, Dixon, Kiene and Allen.[7] Ginzberg [8] suggested that it is possible to diagnose the disease process and even to determine its severity by means of encephalography alone. Hermann and Herrnheiser [9] stated that patients with dementia paralytica who have auditory hallucinations show encephalographic evidence of selective atrophy of the temporal lobe.

Caution must be exercised, however, against the too liberal interpretation of abnormal encephalograms as evidence of cerebral pathologic changes. For example, it is fairly well agreed [10] that failure of the ventricles to fill with air is not necessarily abnormal. Dahl-Iversen [11] said that this failure is observed normally in from 20 to 30 per cent of all encephalograms. Films taken one or two days after the initial films may show the ventricles filled with air.

Air may enter the subdural instead of the subarachnoid space,[12] and its appearance in the encephalogram may be interpreted erroneously

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11. Dahl-Iversen, E.: Valeur diagnostique, dangers et complications de l'encéphalo-ventriculographie, Lyon chir. **30**:671 (Nov.-Dec.) 1933.

12. (*a*) Goette, K.: Ueber die Dartsellung des Encephalogramms und seine Grenzen des Normalen und Pathologischen, Deutsche Ztschr. f. Nervenh. **110**:9, 1929. (*b*) Stone, R. S., and Jones, O. W., Jr.: Encephalography, Radiology **21**:411 (Nov.) 1933. (*c*) Howard, Campbell: Observations on Encephalography, Am. J. Roentgenol. **32**:301 (Sept.) 1934. (*d*) Glaser, M. A.: Encephalography —Its Diagnostic and Therapeutic Value, with Some Remarks on Subdural Air, West. J. Surg. **42**:587 (Oct.) 1934. (*e*) Cramer, Fritz: A Note on the Occurrence and Significance of Air in the Subdural Space After Encephalography, Bull. Neurol. Inst. New York **3**:506 (March) 1934. (*f*) Pendergrass, E. P.: Encephalography: An Explanation of a Possible Error in Technique, Am. J. Roentgenol. **25**:754 (June) 1931. Flügel.[10b] Kruse.[10c] Dahl-Iversen.[11]

as evidence of cortical atrophy. These variations of the normal encephalogram have never been adequately studied. With this in view, we have examined 800 encephalograms in order to determine the frequency of occurrence of air in the subdural space and nonvisualization of the ventricles. We have noted also the relationship of the presence of air in the subdural space to the amount of fluid removed and the postoperative morbidity and mortality.

MATERIAL AND METHODS

Eight hundred encephalograms were obtained from 632 patients for whom the following diagnoses were made:

Diagnosis	Number
Syphilis of central nervous system	252
Epilepsy	121
Posttraumatic psychosis	87
Mental deficiency	61
Postencephalitis	37
Organic psychosis	31
Tumor of the brain	20
Hydrocephalus	19
Diabetes insipidus	4
Total	632

In obtaining the encephalograms the patients were usually given a sedative and then placed in the sitting position for the remainder of the procedure. The two needle method of injecting air was used in the majority of cases. The occasional use of only one needle apparently had no effect on the final results. Extensive manipulation of the head was always resorted to in an effort to remove as much fluid as possible.

Films were taken with the head in the vertical position and always within an hour after the completion of the injection of air. As Pendergrass [12f] has pointed out, air may enter the subdural space after one hour, and the taking of the films must not be delayed beyond that time. In reading the films we depended on Pendergrass' criteria for determining that air has entered the subdural space —evidence of air in the subtentorial space and collapsed ventricles and absence of convolutional markings in the presence of a collection of air over the vertex. The difference in appearance between cortical atrophy (fig. 1) and subdural air (fig. 2) is clearly shown in the illustrations.

RESULTS

Four hundred and forty-eight (56 per cent) of the 800 encephalograms showed normal ventricles and subarchnoid spaces. Forty-eight (6 per cent) of the encephalograms failed to show any air in the cranial cavity, and no interpretation could be made in those cases (table 1).

Air in the Subdural Space.—One hundred and sixty (20 per cent) showed the presence of air in the subdural space. This was bilateral twice as frequently as it was unilateral.

In order to determine the relationship of the presence of air in the subdural space to the severity of the postoperative reaction and to the

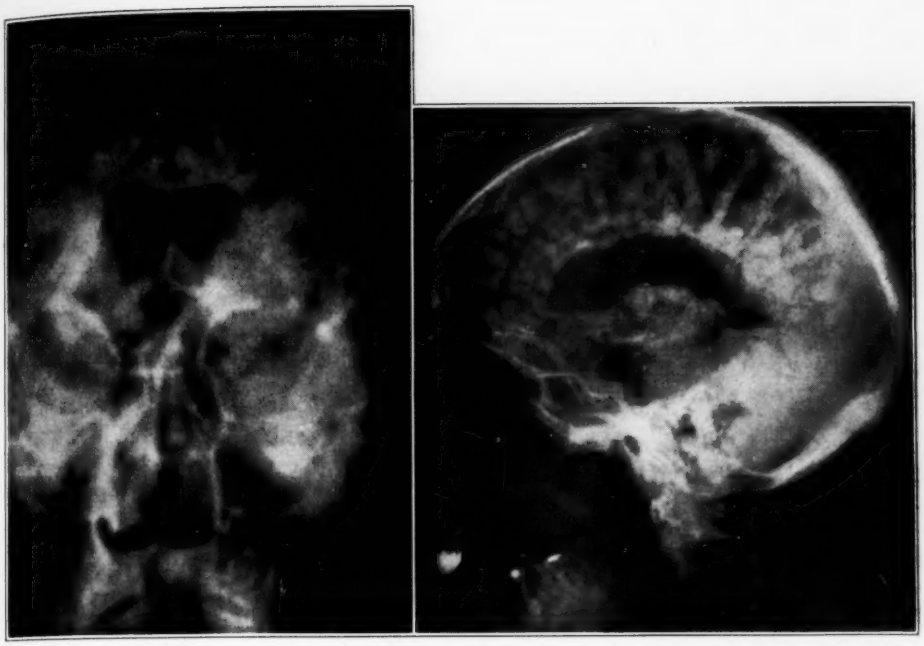

Fig. 1.—Cortical atrophy in a patient with paresis (R. S.). Frontal and lateral views, 250 cc. of fluid having been removed.

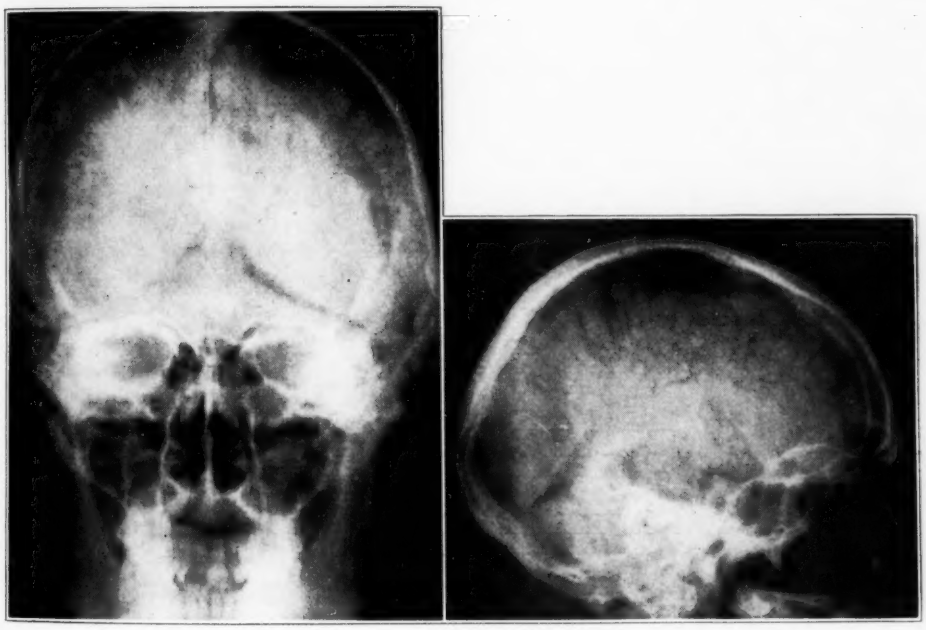

Fig. 2.—Encephalograms taken on Nov. 18, 1933, showing subdural air, predominantly unilateral, in a patient with diabetes insipidus (L. C.). The ventricles are not visualized, and there is subtentorial air. Frontal and lateral views, 120 cc. of fluid having been removed.

amount of air injected, 42 patients were examined. They were chosen because 2 comparable encephalograms, 1 showing air in the subarachnoid and the other in the subdural space, had been obtained from each patient within the period of one year. Table 2 summarizes the results of this part of the investigation.

From table 2 it will be seen that the amount of fluid removed has little to do with either the severity of the postoperative reaction or the

TABLE 1.—*Analysis of Eight Hundred Encephalograms*

Encephalographic Observation		Percentage
Normal subarachnoid spaces and ventricles		56.0
No air		6.0
Hydrocephalus		4.0
Cortical atrophy		5.5
Cerebellar atrophy		0.5
Subdural air		20.0
Unilateral	6.0	
Bilateral	12.0	
Subtentorial air alone	2.0	
Nonvisualized ventricles		8.0
Bilateral	3.0	
Unilateral	2.0	
With subdural air	3.0	

TABLE 2.—*Analysis of Forty-Two Cases in Which Comparable Repeat Encephalograms Were Obtained*

	Average Amount of Fluid Removed, Cc.	Average Reaction on Basis of 4+
Subdural air	134	2+
Subarachnoid air	129	1+

TABLE 3.—*Mortality Statistics in Relation to Eight Hundred Encephalograms*

	Number of Encephalograms	Mortality, Percentage
Subarachnoid air	640	1.2
Subdural air	160	3.1

presence of air in the subdural space. As a fact, in 19 of the 42 cases less air was injected in the instance in which the encephalogram showed air in the subdural space than in that in which the air penetrated into the subarachnoid space (figs. 2 and 3).

The postoperative reactions in cases in which the air entered the subdural space were twice as severe as those in cases in which the air went into the subarachnoid space. Mortality statistics (table 3) give further confirmation of the association of the entrance of air into the subdural space with severe postoperative reactions (death occurred less than one month after encephalography).

An analysis of the 42 cases in which comparable repeat encephalograms were obtained gives important information as to the significance of the entrance of air into the subdural space. For example, in 24 of the 42 cases subdural air was demonstrated in the first but not in the second encephalogram. In 18 of these 24 cases the second encephalogram showed normal subarachnoid spaces and ventricles (figs. 4 and 5), while in 6 cases the second encephalogram showed cortical atrophy. From this it is apparent that the entrance of air into the subdural space may be associated with underlying cortical atrophy. On the other hand,

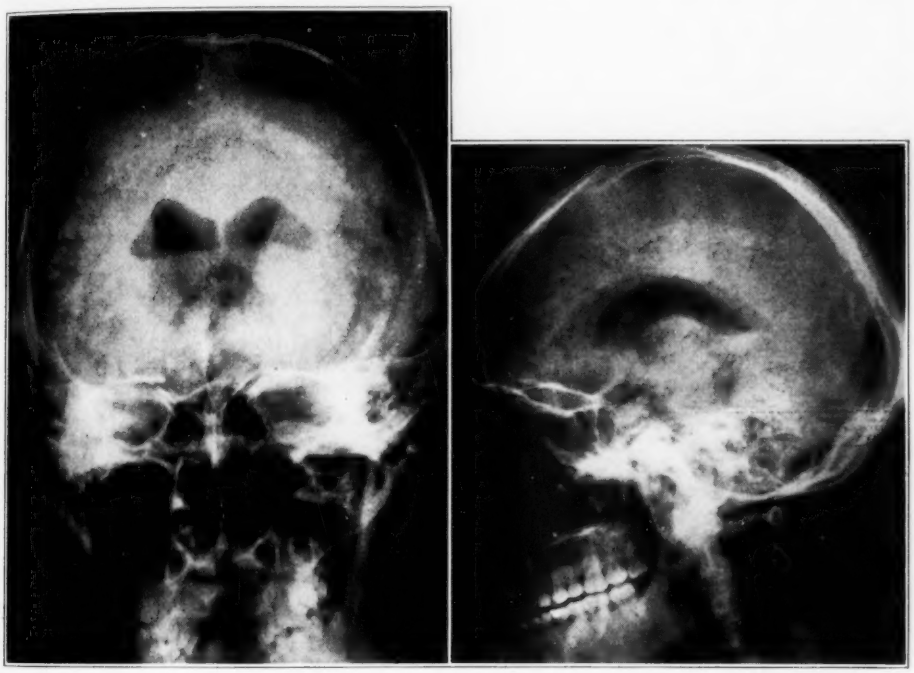

Fig. 3.—Normal subarachnoid spaces and ventricles (L. C.). These encephalograms were obtained on Aug. 30, 1934, about ten months after those shown in figure 2. Frontal and lateral views, 145 cc. of fluid having been removed.

the entrance of air into the subdural space does not necessarily indicate that organic changes have taken place, and a second subsequent encephalogram may be entirely normal. There is no absolute method of determining whether the entrance of air into the subdural space is secondary to cortical atrophy or a technical error, but roentgen evidence of subtentorial air and collapsed ventricles suggests the latter in any particular case. Lack of evidence of air in the subdural space in an encephalogram does not preclude its visualization in subsequent encephalograms (figs. 6 and 7).

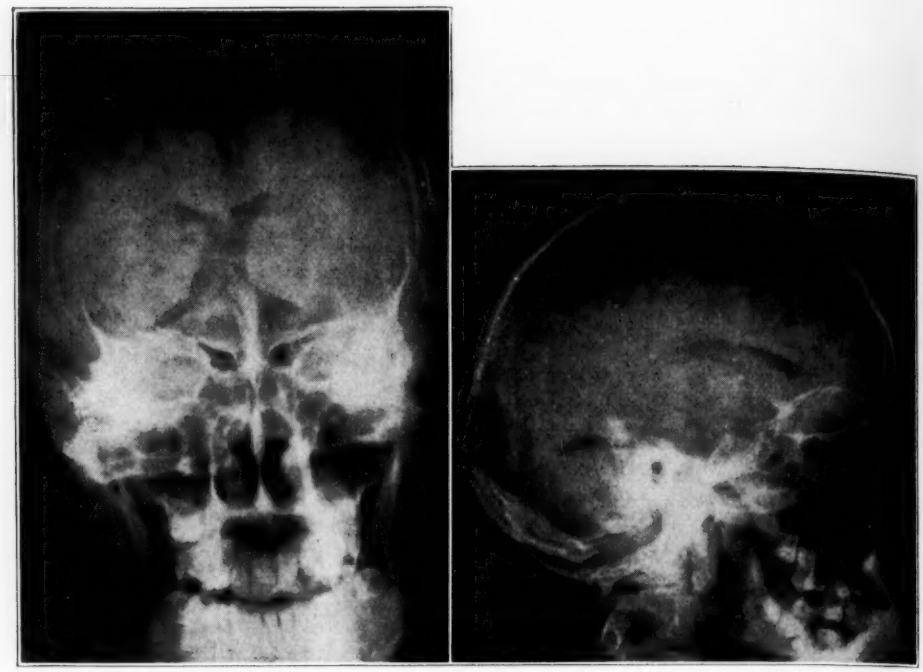

Fig. 4.—Encephalograms taken on Jan. 17, 1934, showing subdural air in a patient with epilepsy (A. B.). Frontal and lateral views, 195 cc. of fluid having been removed.

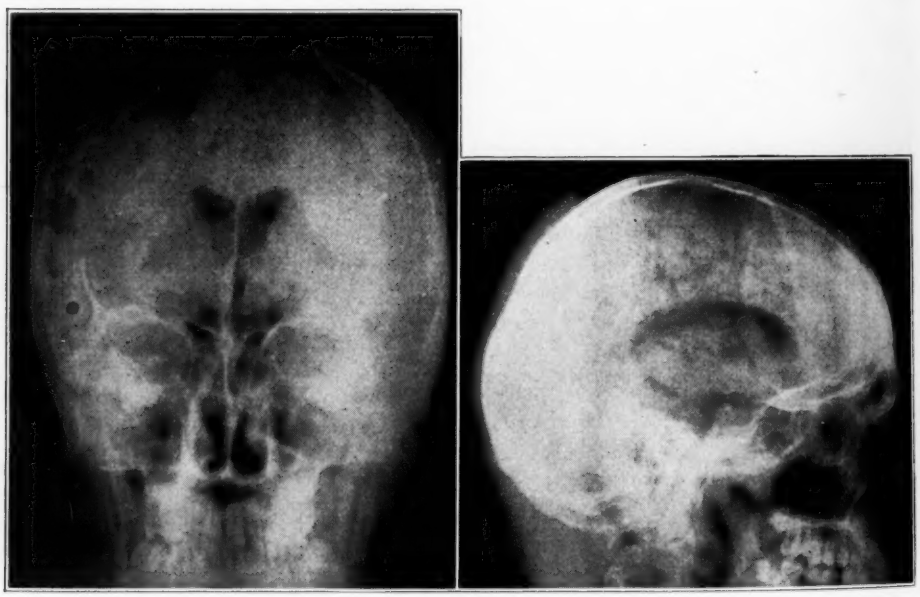

Fig. 5.—Normal subarachnoid spaces and ventricles (A. B.). These encephalograms were obtained on Feb. 12, 1934, about one month after those shown in figure 4. Frontal and lateral views, 165 cc. fluid having been removed.

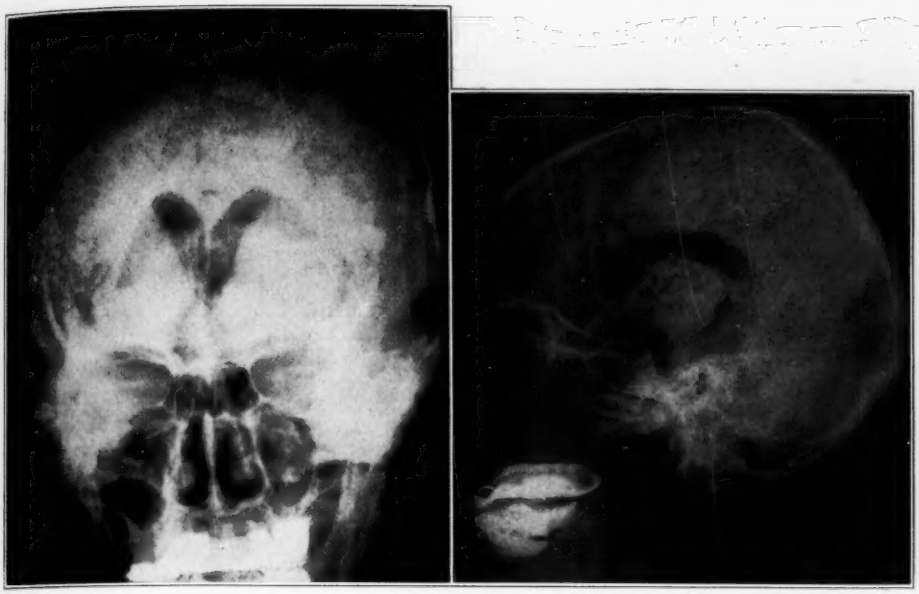

Fig. 6.—Normal subarachnoid spaces and ventricles in encephalograms taken on Dec. 4, 1930, of a patient (M. D.) with paresis. Frontal and lateral views, 160 cc. of fluid having been removed.

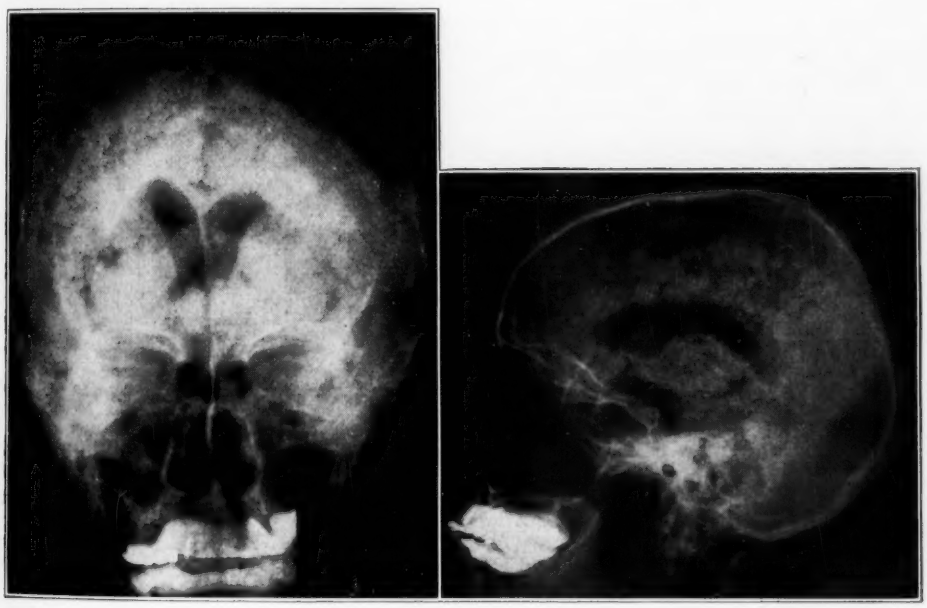

Fig. 7.—Subdural air (unilateral) (M.D.). These encephalograms were obtained on Jan. 14, 1931, about one and one-half months after those shown in figure 6. Frontal and lateral views, 165 cc. of fluid having been removed.

Failure of Ventricles to Fill with Air.—The ventricles failed to contain air in 64 (8 per cent) of the encephalograms (table 1). This failure was bilateral in approximately two thirds of the 64 cases.

Air in the Subtentorial Space and Cerebellar Atrophy.—Sixteen (2 per cent) of the encephalograms showed subdural air in the subtentorial space alone. The air was located above the cerebellum (fig. 8) and must not be interpreted as evidence of cerebellar atrophy. In cases of cerebellar atrophy the air lies posterior to the cerebellum (fig. 9). Air in the subtentorial space is visualized in the anteroposterior films, while the presence of air due to cerebellar atrophy is usually not shown in that projection. Many encephalograms suggest a collection of air in the suboccipital area, but a diagnosis of cerebellar atrophy should be reserved for cases in which a relatively large amount of air is visualized in that location. Three such instances (0.5 per cent) were found in the 800 encephalograms; 2 were cases of mental deficiency and 1 was associated with posttraumatic psychosis.

COMMENT

Thus far the entrance of air into the subdural space has been assumed on the basis of encephalographic findings alone. Postmortem examinations in 2 of our cases of death within three days after encephalography, however, confirmed the antemortem diagnosis of the entrance of air into the subdural space (fig. 10). Cramer [12e] reported a case in which air was actually found to be present in the subdural space at the time of a trephine operation performed the day after encephalography. Air was found in the subdural space in 1 of our patients on whom trephination was performed by Dr. J. R. Jaeger because of a severe reaction following encephalography. In this case, replacing the air, which was not under pressure, with physiologic solution of sodium chloride failed to prevent death.

There are several theories as to why the air enters the subdural space instead of the subarachnoid space in some cases. Pendergrass [12f] said that in the majority of cases in which this occurs the air has been injected directly into the subdural space through the lumbar puncture needle. He suggested that the needle may have punctured the arachnoid, allowing the cerebrospinal fluid to escape into the subdural space around the tip of the needle. Goette [12a] concurred with this theory, and Stone and Jones [12b] have produced evidence from experiments with cadavers that air injected into the subdural space through the lumbar puncture needle may extend into the subdural spaces of the skull. On the other hand, the same experiments of Stone and Jones indicated that it is much more likely that air enters the subdural space through a tear in the arachnoid membrane. As Glaser [12d] has pointed out, it is difficult to understand how air gets into the ven-

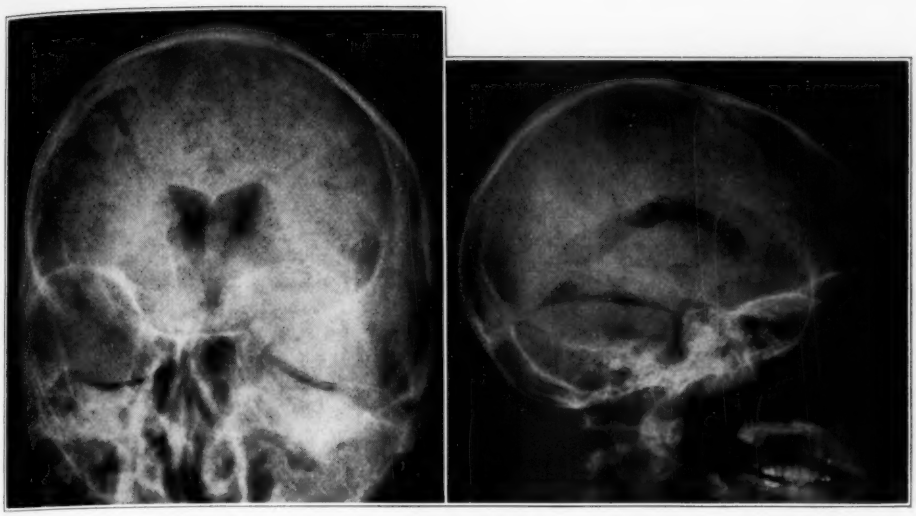

Fig. 8.—Subdural air limited to the subtentorial space in a postencephalitic patient (A. M.). One hundred and thirty cubic centimeters of fluid was removed. Subtenorial air is seen above the cerebellum in the lateral view and as laterally sloping collections of air in the frontal view.

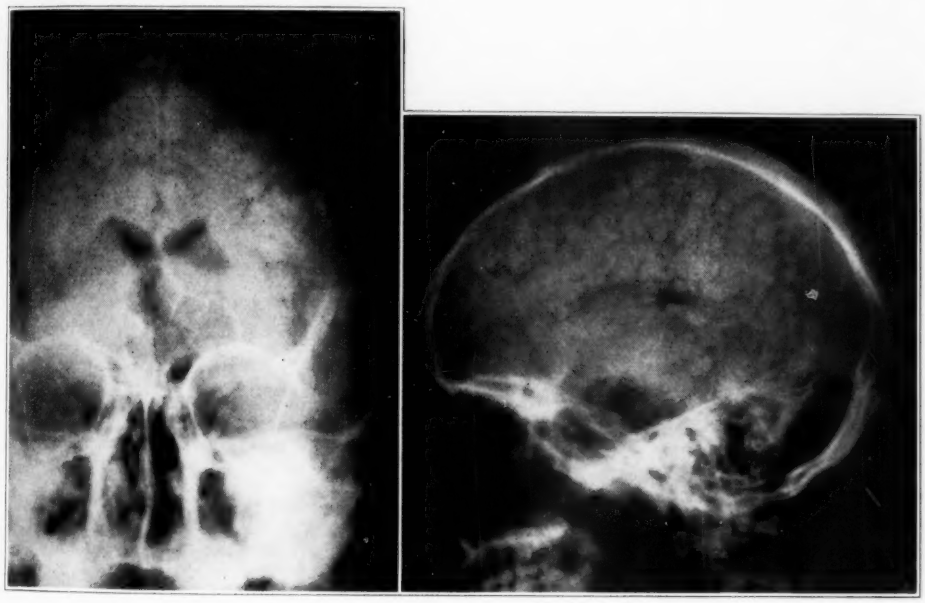

Fig. 9.—Cerebellar atrophy in a patient (J. B.) with a posttraumatic psychosis. One hundred and fifty cubic centimeters of fluid was removed. Air is seen suboccipital and posterior to the cerebellum in the lateral film, but it is not obvious in the frontal projection.

tricles if it is injected directly into and remains within the subdural space. Our own opinion is that the air enters the subdural space through tears in the arachnoid. The high percentage of instances of roentgen evidence of subdural air in our series may be due to our technic of extensive manipulation of the head and efforts to remove large quantities of fluid, procedures which certainly would tend to produce tears in the arachnoid membrane.

There has been little explanation of why the ventricles fail to contain air in some encephalograms. One theory is that a thin membrane

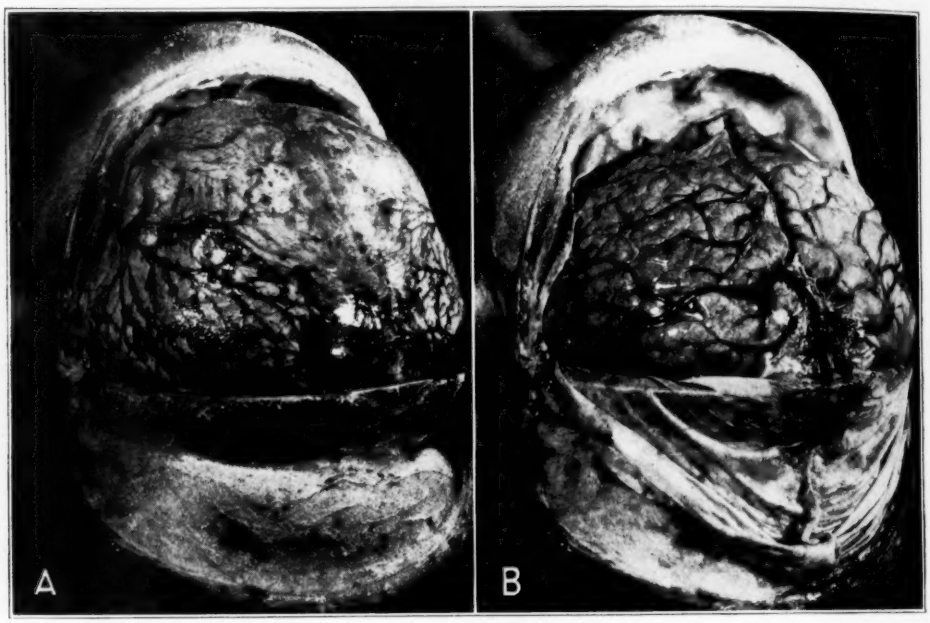

Fig. 10.——Postmortem appearance of the brain of a patient (C. R.) with paresis who died three days after encephalography. *A* shows the dura distended with air; *B*, the intact arachnoid (the dura having been removed), with no evidence of subarachnoid air.

(Bateman [13]) covers the foramina of Magendie and Luschka and sometimes prevents air from entering the ventricles. Another theory suggests that the ventricles may collapse and thus not be visualized. Few films not showing ventricles, however, give any evidence of a sinking in of the cortex, such as would be expected to accompany collapse of the ventricles. The collapse of the ventricles underlying the subdural

13. Bateman, J. F.: Closed Foramina of Luschka in the Brains of the Insane: Their Influence on the Pathogenesis of the Psychoses, Arch. Neurol. & Psychiat. **14**:616 (Nov.) 1925.

space containing air is probably due to a purely mechanical process. A collection of air in the subdural space over the vertex must displace the brain downward and compress the ventricles, unless there is already a certain amount of underlying cortical atrophy. Nonvisualization of the ventricles is noted twice as frequently in association with air in the subdural space as without it.

SUMMARY AND CONCLUSIONS

There is a tendency in present-day literature to diagnose a pathologic condition of the brain on the basis of abnormal encephalograms alone. As the normal variations and technical difficulties of encephalography have never been sufficiently studied, interpretation of organic changes must be made cautiously. For this reason we have examined 800 encephalograms with special reference to the entrance of air into the subdural space and nonvisualization of the ventricles. The results of this study were as follows:

Twenty per cent of the encephalograms showed air in the subdural space. The actual presence of air in the subdural space was demonstrated ante mortem (trephine) in 1 case and post mortem in 2 cases.

The amount of fluid removed apparently had little relation to the presence of air in the subdural space or to the severity of the postoperative reaction.

The postoperative reactions were about twice as severe in patients showing air in the subdural space as in those showing air in the subarachnoid space. The mortality rate was higher for patients showing air in the subdural space.

The entrance of air into the subdural space may be associated with an underlying cortical atrophy or may be due to a technical error. The latter condition is more likely when air in the subtentorial space and collapsed ventricles are also present.

Air probably enters the subdural space through tears in the arachnoid membrane. Manipulations of the head during encephalography may increase these tears.

The ventricles were not visualized in 8 per cent of 800 encephalograms. This was noted twice as frequently in cases in which the air entered the subdural space as in cases in which it entered the subarachnoid space.

A diagnosis of cerebellar atrophy was made in 3 cases in which there was a relatively large collection of air lying posterior to the cerebellum. This must be differentiated from conditions in which there is a collection of air in the subdural space lying over the cerebellum and under the tentorium.

RESPONSE OF CEREBRAL BLOOD VESSELS TO ELECTRIC STIMULATION OF THE THALAMUS AND HYPOTHALAMIC REGIONS

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MONTREAL, CANADA

The analysis of the literature on cerebral circulation recently published by Forbes and Wolff [1] demonstrates the variability of results obtained in this field by different investigators. Inability to obtain active vasomotor responses from the intracranial blood vessels led many to assume that these vessels possess no effective neural control (Schiff;[2] Schultz;[3] Riegal and Jolly;[4] Gaertner and Wagner;[5] Bayliss and Hill;[6] Hill;[7] Hill and MacLeod;[8] Gerhardt;[9] Roy and Sherrington;[10] Florey,[11] and others).

However, histologic evidence pointing toward the existence of autonomic nerve fibers and nerve endings on the pial and cerebral

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From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

Read by title at the Sixty-First Annual Meeting of the American Neurological Association, Montreal, Canada, June 5, 1935.

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11. Florey, H. W.: Microscopical Observations on the Circulation of the Blood in the Cerebral Cortex, Brain **48**:43, 1925.

blood vessels (Obersteiner;[12] Gulland;[13] Morrison;[14] Kölliker;[15] Huber;[16] Hunter;[17] Stöhr;[18] Clarke;[19] Hassin,[20] and Penfield[21]) supported the accumulating experimental evidence favoring the probability of an active nervous control over these vessels, and only the extreme inconstancy of the obtained results delays the final conclusion on this matter.

Applying different methods of investigation, most commonly direct observation of the arteries and veins, measurements of variations in the volume of the brain and studies of pressure and speed of flow in the intracranial vascular bed, a multitude of investigators were led to the conviction that these blood vessels, though reacting in a somewhat unusual way, still possess the property of active constriction and dilatation.[22] Improved methods of observation of the pial blood vessels recently devised by Forbes[23] and the studies carried out by this method[24] have added valuable information about cerebral circulation

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12. Obersteiner, O.: Arb. a. d. Inst. f. Anat. u. Physiol. d. Centralnervensyst. a. d. Wien. Univ. **5**:215, 1897.

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14. Morison, A.: On the Innervation of Intracranial Vessels, Edinburgh M. J. **4**:413, 1898.

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22. For the complete list of references to the earlier work see Forbes and Wolff.[1]

23. Forbes, H. S.: Cerebral Circulation: I. Observation and Measurement of Pial Vessels, Arch. Neurol. & Psychiat. **19**:751 (May) 1928.

24. (*a*) Forbes, H. S., and Wolff, H. G.: Cerebral Circulation: V. Observations of the Pial Circulation During Changes in Intracranial Presure, Arch. Neurol. & Psychiat. **20**:1035 (Nov.) 1928. Forbes and Wolff.[1] (*b*) Wolff, H. G., and Blumgart, H. L.: Cerebral Circulation: VI. The Effect of Normal and of Increased Intracranial Cerebrospinal Fluid Pressure on the Velocity of Intracranial Blood Flow, ibid. **21**:795 (April) 1929. (*c*) Talbott, J. H.; Wolff, H. G., and Cobb, S.: Cerebral Circulation: VII. Changes in Cerebral Capillary Bed Following Cervical Sympathectomy, ibid. **21**:1102 (May) 1929. (*d*) Forbes, H. S.; Wolff, H. G., and Cobb, S.: Cerebral Circulation: X. The Action of Histamine, Am. J. Physiol. **89**:266, 1929. (*e*) Wolff, H. G.: Cerebral Circula-

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and have experimentally established beyond reasonable doubt the existence of vasomotor nerves to the pial vessels as well as the active nature of their responses to alterations in gaseous metabolism and to various pharmacologic agents.

In spite of the great amount of work done on the peripheral parts of the neurovascular mechanism of the brain and meninges, few attempts have been made to study the response of the cerebral vessels to stimulation of the vasomotor centers. Gaertner and Wagner [5] studied the effect of stimulation of the vasomotor center by strychnine and asphyxia on the venous return from the brain and believed that it was possible to explain all the observed changes on a mechanical basis and did not favor the supposition of any influence of the vasoconstrictor centers on the cerebral blood vessels. Florey,[11] stimulating electrically the vasomotor center in the medulla, could see no change in the cerebral blood vessels. However, evidence also accumulated favoring the existence of a reflex control of the intracranial blood vessels. Spina [25] when stimulating the medulla with faradic current could see dilatation of the pial arteries, which effect persisted after interruption of the peripheral part of the hindbrain.

Gesell and Bronk,[26] using a thermocouple to determine the volume of the flow of blood in the carotid and femoral arteries and artificially adjusting the mean blood pressure at a constant level, stimulated the vasomotor centers by means of a high intake of carbon dioxide or oxygen. With this method they could see differences in the responses of the two arteries which suggested to them an active adjustment taking place with benefit to the brain, and the direct observations of pial vessels by Wolff and Lennox [24f] stand in agreement with these findings. Nothnagel,[27] Krauspe,[28] Schüller,[29] Meyer and Pribram [30]

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tion: XIa. The Action of Acetylcholine, Arch. Neurol. & Psychiat. **22**:686 (Oct.) 1929. (*f*) Wolff, H. G., and Lennox, W. G.: Cerebral Circulation: XII. The Effect on the Pial Vessels of Variations in the Oxygen and Carbon Dioxide Content of the Blood, ibid. **23**:1097 (June) 1930. (*g*) Finesinger, J. E.: Cerebral Circulation: XVIII. Effect of Caffeine on Cerebral Vessels, ibid. **28**:1290 (Dec.) 1932. (*h*) Forbes, H. S.; Finley, K. H., and Nason, G. J.: Cerebral Circulation: XXIV. A. Action of Epinephrine on Pial Vessels; B. Action of Pituitary and Pitressin on Pial Vessels; C. Vasomotor Response in the Pia and in the Skin, ibid. **30**:957 (Nov.) 1933. (*i*) Clark, G. A., and Wall, T. F.: Unconsciousness Produced by Electric Currents, Quart. J. Exper. Physiol. **24**:85, 1934.

25. Spina, A.: Wien. med. Bl. **21**:247, 1898; Experimentelle Untersuchungen über die Bildung des Liquor cerebrospinalis, Arch. f. d. ges. Physiol. **76**:204, 1899.

26. Gesell, R., and Bronk, D. W.: Some Effects of Alveolar Carbon Dioxide Tension on the Carotid and Femoral Flow of Blood, Proc. Soc. Exper. Biol. & Med. **24**:255, 1926.

27. Nothnagel, H.: Die vasomotorischen Nerven der Gehirngefässe, Virchows Arch f. path. Anat. **40**:203, 1867.

and Jacobi and Magnus [31] observed a constriction of the pial blood vessels on stimulation of sensory nerves which suggested a possibility of reflex constriction of these vessels.

Reiner and Schnitzler,[32] von Cyon,[33] Roy and Sherrington,[10] Müller and Siebeck,[34] Weber,[35] Anrep and Starling,[36] Forbes and Wolff [1] and Cobb and Finesinger [37] have seen vasodilatation in the brain and leptomeninges on stimulation of the central end of the vagus nerve. The last two investigators concluded that this vasodilatation was the result of a medullary reflex for which the facial nerves were serving as the effector paths, and Chorobski and Penfield [38] were able to support this supposition by the demonstration of an anatomic pathway from the facial nerve to the internal carotid artery.

In the meantime clearer and more accurate information concerning the localization of higher centers for the autonomic nervous system has been acquired. The earlier indications of Danilewski,[39] Nussbaum,[40] Klug,[41] Ott and Field,[42] Prus,[43] Bechterew,[44] Affanasiew,[45]

28. Krauspe, F.: Ueber die reflectorische Beeinflussung der Piaarterien, Virchows Arch. f. path. Anat. **59**:472, 1874.

29. Schüller, M.: Ueber die Einwirkung einiger Arzneimittel auf die Gehirngefässe, Berl. klin. Wchnschr. **11**:294, 1874.

30. Meyer, A., and Pribram, E., quoted from Rosenthal: Klinik der Nervenkrankheiten, Stuttgart, Ferdinand Enke, 1875, p. 97.

31. Jacobi, W., and Magnus, G.: Arch. f. Psychiat. **74**:126, 1923.

32. Reiner, M., and Schnitzler, T.: Beitrag zur Kenntnis der Blutcirculation im Gehirn, Arch. f. exper. Path. u. Pharmakol. **38**:249, 1896-1897.

33. von Cyon, E.: Die physiologischen Herzgifte, Arch. f. d. ges. Physiol. **74**: 97, 1899.

34. Müller, O., and Siebeck, R.: Ueber die Vasomotoren des Gehirns, Ztschr. f. exper. Path. u. Therap. **4**:57, 1907.

35. Weber, E.: Ueber die Selbständigkeit des Gehirns in der Regulierung seiner Blutversorgung, Arch. f. Physiol., 1908, p. 457.

36. Anrep, G. V., and Starling, E. H.: Central and Reflex Regulation of the Circulation, Proc. Roy Soc., London, s.B **97**:463, 1924-1925.

37. Cobb, S., and Finesinger, J. E.: The Vagal Pathway of the Vasodilator Impulses, Arch. Neurol. & Psychiat. **28**:1243 (Dec.) 1932.

38. Chorobski, J., and Penfield, W.: Cerebral Vasodilator Nerves and Their Pathway from the Medulla Oblongata, with Observations on the Pial and Intracerebral Vascular Plexus, Arch. Neurol. & Psychiat. **28**:1257 (Dec.) 1932.

39. Danilewski, B.: Experimentelle Beiträge zur Physiologie des Gehirns, Arch. f. d. ges. Physiol. **11**:128, 1875.

40. Nussbaum: Arb. a. d. Lab. v. Nawrocki, 1879, no. 5; quoted from Bechterew, W. V.: Die Functionen der Nervencentra, Jena, Gustav Fischer, 1908-1911, vol. 2, p. 1161.

41. Klug, F.: Ueber den beschleunigenden Einfluss des Nerven Vagus auf die Herzbewegung, Arch. f. Physiol., 1880, p. 506.

42. Ott, I., and Field: J. Nerv. & Ment. Dis. **4**:654, 1879. Ott, I: ibid. **12**:152, 1887; **14**:457, 1889; **16**:431, 1891; **20**:773, 1893.

(Footnotes continued on next page)

Ekkhardt,[45] Sachs [46] and others pointing to the important rôle of the diencephalon in the regulation of the functions of lower autonomic centers have been substantiated by the more recent physiologic studies of Karplus and Kreidl,[47a] Winkler,[47b] Aschner,[48] Schrottenbach.[49] Lewy,[45] Gerstmann,[50] Lichtenstern,[51] Isenschmid and Krehl,[52] Isenschmid and Schnitzler,[53] Keller,[54] Bard,[55] Fulton and Ingraham,[56] Morgan,[57] Beattie, Brow and Long,[58] Beattie,[59] Ranson and his co-workers [60] and

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43. Prus, J.: Ueber die bei electrischer Reizung des Corpus striatum und des Thalamus opticus auftretenden Erscheinungen, Wien. klin. Wchnschr. **12**:1199, 1899.

44. Bechterew, W. V., and Mislavski, N.: Arch. psikhiat., 1886 and 1888; Neurol. Centralbl. **8**:190, 1889; Med. Obozr., 1891. Bechterew, W. V.: Die Functionen der Nervencentra, Jena, Gustav Fischer, 1908-1911, vol. 2, p. 1105.

45. Affanasiew, also Ekkhardt, and Lewy, quoted from Greving, R., in Müller, L. R.: Lebensnerven und Lebenstriebe, ed. 3, Berlin, Julius Springer, 1931, p. 176.

46. Sachs, E.: Brain **32**:95, 1909; J. Exper. Med. **14**:408, 1911.

47. (*a*) Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus, I-VII, Arch. f. d. ges. Physiol. **129**:138, 1909; **135**:401, 1910; **143**:109, 1912; **171**:192, 1918; **203**:533, 1924; **215**:443 and 667, 1926-1927. (*b*) Winkler, C.: ibid. **125**: 584, 1908. (*c*) Karplus, J. P.: Arch. f. Physiol., 1914, p. 165; Wien. klin. Wchnschr. **29**:31, 1916; Arch. f. d. ges. Physiol. **207**:134, 1918; Wien. klin. Wchnschr. **43**:622, 1930; Jahrb. f. Psychiat. u. Neurol. **50**:11, 1933.

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53. Isenschmid, R., and Schnitzler, W.: Arch. f. exper. Path. u. Pharmakol. **76**:202, 1914.

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57. Morgan, L. O.: The Nuclei of the Region of the Tuber Cinereum, Arch. Neurol. & Psychiat. **24**:267 (Aug.) 1930.

58. Beattie, J.; Brow, G. R., and Long, C. N. H.: Proc. Roy. Soc., London, s.B **106**:253, 1930; A. Research Nerv. & Ment. Dis., Proc. **9**:249 and 297, 1930.

59. Beattie, J.: The Relation of the Tuber Cinereum to Gastric and Cardiac Function, Canad. M. A. J. **26**:278, 1932; Hypothalamic Mechanisms, ibid. **26**:400, 1932.

60. (*a*) Ingram, W. R.; Ranson, S. W., and Hannett, F. I.: Pupillary Dilatation Produced by Direct Stimulation of the Tegmentum of the Brain Stem, Am. J.

many other investigators. These researches allow the higher autonomic centers to be placed with a certain amount of probability in the region of the hypothalamus.

Anatomohistologic studies [61] of this significant part of the central nervous system, its cell groups, fiber connections and relation to lower

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Physiol. **98**:687, 1931. (*b*) Ingram, W. R.; Ranson, S. W.; Hannett, F. I.; Zeiss, F. R., and Terwilliger, E. H.: Results of Stimulation of the Tegmentum with the Horsley-Clarke Stereotaxic Electrode, Arch. Neurol. & Psychiat. **28**:513 (Sept.) 1932. (*c*) Ranson, S. W., and Magoun, H. W.: Respiratory and Pupillary Reactions Induced by Electrical Stimulation of Hypothalamus, ibid. **29**:1179 (June) 1933. (*d*) Ranson, S. W.; Kabat, H., and Magoun, H. W.: Autonomic Responses to Electrical Stimulation of Hypothalamus, Preoptic Region and Septum, ibid. **33**: 467 (March) 1935.

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centers, though as yet lacking in clarity and a standardized nomenclature, have added much to the understanding of the physiology of the hypothalamus and of the diencephalon as a whole and seem to justify the aforementioned conception.

Being a comparatively large, more or less isolated region of the brain, the hypothalamus seemed more suitable for experiments with electric stimulation than the lower vasomotor centers, and it was suggested by Dr. Wilder Penfield that I explore this region and the thalamus as well with tetanizing currents and at the same time study the reaction of the pial blood vessels to such stimulation. The results of this investigation will be reported presently.

METHODS

Cats under light dial anesthesia were used, 0.3 to 0.4 cc. of dial per kilogram of body weight having been injected intraperitoneally. Occasionally during the dissection some ether had to be given in addition. Large doses of dial markedly reduced the effectiveness of the stimulations. Under ether and chloroform the size of the pial arteries varied considerably and the results were inconclusive. Chloralose caused swelling of the brain and made the operative procedure most difficult; only with sedative doses of dial, combined with ether during the dissection, were satisfactory results obtained. Tracheotomy, cannulation of the femoral artery, dissection of sympathetic ganglia, laminectomy and other preparatory operative procedures were done before the experiment. The animal was then placed in the Gage head-holder and a window adjusted over the right hemisphere of the brain. Lastly, a parieto-occipital trepanation on the left side of the head was performed, the dura was split open along the sagittal sinus and turned down, and the parieto-occipital part of the hemisphere was exposed. The veins entering the sagittal sinus were ligated, the hemisphere was retracted, a small moist sponge was applied over the vein of Galen to prevent its tearing, and an incision from 1 to 1.5 cm. long was made in the corpus callosum. The choroid plexus of the third ventricle being then in sight, it was dissected from the left thalamus by a small sponge and pushed over to the right. After this manipulation the posterior part of the third ventricle became visible. The middle and posterior commissures and the thalami serving as landmarks, a flexible bipolar electrode, 1 mm. in diameter, could be placed in each hypothalamus or thalamus with a considerable degree of accuracy and kept in place by small moist sponges and the weight of the left hemisphere. For the stimulation of the external parts of the tuber cinereum the left temporal lobe was elevated and a curved electrode was placed into or at the tuber and kept in place by the weight of the brain, better results being obtained that way than when the electrode was introduced from the midline.

Slow, careful dissection was found to give better results than rapid manipulation, and after the electrode was put in place the animal was given time to recover before the experiment began. During the experiment the position of the electrode could be changed two or three times, if necessary, without much damage to the brain. Bloodless operating is most important in experiments of this type and cannot be overstressed.

Stimulation was carried out either by means of an induction coil (two dry cells being attached to the primary circuit) or by means of a thyratron stimulator,

designed by Schmitt and Schmitt,[62] set at a frequency of from 60 to 70 shocks per second, the strength of current varying according to need but seldom exceeding that endurable on the tip of the tongue. Kymographic tracings of blood pressure and respirations were taken and measurements of the pial arteries made according to Forbes'[23] technic. Changes in the size of the pupils, pilo-erection, salivation, lacrimation and micturition were recorded when seen. At the end of most of the experiments the brain was taken out, fixed in solution of formaldehyde U. S. P. (1:10), and frozen sections, 20 to 40 microns thick, were cut in the frontal plane, mounted on slides in gelatin, dried in a thermostat containing formaldehyde solution vapor and stained with cresyl violet like ordinary paraffin sections; after histologic study the position of the electrode was recorded. Eleven experiments were also done with the stereotaxic electrode of Horsley and Clarke,[63] but the difficulty of observation of the pial arteries with the animal's head in the instrument and the disadvantage of launching the electrode through the hemisphere and thalamus before reaching the desired region led to abandonment of this method and to the use of the technic described. The experiments performed with the stereotaxic instrument are not included in the present series as no constriction of the pial arteries was obtained with this technic.

EXPERIMENTAL RESULTS

It must be stated at the beginning that stimulation of the peripheral end of the cervical sympathetic trunk on many occasions has been seen to produce diminution of the size of pial arteries, ranging mostly from 10 to 15 per cent. This effect was homolateral and required the application of stronger currents than those needed to produce pupillary dilatation. The constriction of the arteries came on after a longer latent period than the dilatation of the pupil, and the after-effect often considerably outlasted it.

Intravenous administration of epinephrine hydrochloride, solution of posterior pituitary, acetylcholine or histamine was followed by an increase in the size of the pial arteries. In two experiments in which the common carotid artery was ligated on the side of the skull window, however, intravenous injections of epinephrine hydrochloride produced transient constriction of the pial artery which was soon followed by dilatation. Also, local applications of epinephrine in 1:1,000 and 1:10,000 concentrations under the window have been seen to produce constriction of the pial vessels.

Exploration of the Subcortical Regions with Tetanizing Currents.—Experiments with electric stimulation of the subcortical regions of the central nervous system gave the following typical results:

Stimulation of different parts of the thalamus was frequently seen to produce a moderate dilatation of the pupils and a rise of blood pres-

62. Schmitt, O. H., and Schmitt, F. O.: A Universal Precision Stimulator, Science **76**:328, 1932.

63. Horsley, V., and Clarke, R. H.: The Structure and Function of the Cerebellum Examined by a New Method, Brain **31**:45, 1908.

sure, which were accompanied by changes in respiration. These findings agree with the observations of Sachs, the localization in the thalamus coinciding with the data of this investigator so closely that any detailed discussion of it is unwarranted.

In addition to the aforementioned phenomena, dilatation of the pial arteries ranging up to 30 per cent was seen to take place and was most pronounced on stimulation of the ventral and medial parts of the thalamus. If the electrode was gradually lowered it came to a region, a few millimeters broad, from which none of these responses could be obtained. Occasionally a slightly greater force was required in order to push the electrode through this silent area, which probably indicated that the electrode was moved through a region rich in fibers.

Immediately after it was passed, stimulations were followed by a maximal dilatation of the pupils, a much greater rise of blood pressure than that obtained on stimulation of the thalamus, erection of hair, protrusion of claws, salivation, lacrimation, marked increase and acceleration of respiratory movement or apnea, restlessness and running movements or sudden quietness associated often with a curving of the back or stiffening of the tail. When the electrode was at the mesial parts of the cerebral peduncles flexion of one or both lower extremities was observed.

To stimulation of this region the pial arteries were seen to respond by a constriction which, in spite of the rise of the systemic blood pressure, on many occasions was marked, varying in different experiments from 10 to 30 per cent. In cases of very pronounced constriction shrinking of the brain and pallor of the arterial wall were also noted. In most experiments the electrode was not moved any deeper, and its position was later determined on histologic sections. However, in many instances the electrode was lowered still farther. On stimulation 3 or 4 mm. deeper the phenomena of sympathetic excitation disappeared. When the electrode went in front of the mamillary body into the ventral and ventrolateral regions of the tuber cinereum, dilatation of the pial artery was observed. In the lower parts of the most anterior hypothalamic area—the supra-optic region of Beattie—occasionally also some slight variations in the size of the arteries were seen, but the results were not as constant and conclusive as those obtained on stimulation of the tuber. In planes lying caudad to the mamillary body, though effects of sympathetic irritation were obtained on many stimulations, the response of the pial arteries varied so much that no definite impression could be formed as to its type. This is true also of the stimulation of the whole mesencephalon. Stimulations of the caudate nucleus and other higher regions were found on the whole ineffective.

The dilatation of the pial arteries seen on stimulation of the tuber was checked in special experiments in which the temporal lobe was elevated and only the outer surface of the tuber stimulated. The dilatation observed amounted to from 15 to 30 per cent and was accompanied by a transient slowing of the heart and a slight fall of blood pressure. These effects could be elicited with the secondary coil set at from 9 to 11 cm. from the primary one, and even still weaker currents were effective, whereas for the demonstration of sympathetic excitation on stimulation of the dorsal parts of the hypothalamus the coil had to be set at from 7.5 to 9 cm.[64]; weaker currents produced only dilatation of the pupils and some respiratory changes. The region of the tuber was also found to be very sensitive to pressure, and all the aforementioned responses could be seen on slight pressure exerted with a small sponge.

Sometimes two and even three electrodes were placed in the thalamus, hypothalamus and at the outer surface of the tuber, respectively, in the same experiment, and stimulations of these separate regions could be seen to produce different effects. The data to be quoted are characteristic of the results obtained:

Experiment 8, Nov. 16, 1933:[65] The cat weighed 1.6 Kg.; 0.5 cc. of dial was injected intraperitoneally. The pleural cavity was opened and artificial respiration introduced in order to exclude the effect of changes in respiration. A skull window was placed over the right hemisphere. The animal was quiet but conscious of what was going on around it. It could be made to look in the direction of a sound, licked its lips, and withdrew its paws on pinching. The pupils reacted to light, and the corneal reflex was present.

In figure 1, *A* shows the effect of one of the stimulations of the ventrolateral surface of the tuber cinereum. The electrode was lowered through the tip of the temporal pole. The pupils did not dilate, whereas the pial artery, in spite of the fall in blood pressure, dilated from 13 divisions of the scale to 18 divisions. Four minutes after the end of the stimulation the artery resumed its initial size.

In figure 1, *B* and *C* show the effect on the heart as recorded on a rapidly moving drum in experiment 16. This was obtained under direct observation by stimulation of the tuber from without by means of the induction coil and mechanical pressure. The temporal lobe was elevated, and the brain remained completely intact. The pial artery responded to these stimulations also by dilatation.

In figure 2 the effect of stimulation of the medial and ventral part of the right thalamus can be seen (experiment 8, continued). A moderate dilatation of the pupils and an increase of respiratory movements accompanied the rise of blood pressure and dilatation of the pial artery. The latter dilated during the stimulation from 13 to 16 divisions and resumed its initial size one minute and fifteen seconds after the end of the stimulation.

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64. With the electrode used, currents obtained with the coils at 11 cm. distance were barely perceptible on the tip of the tongue; at 7.5 cm. distance the current was still endurable.

65. The position of the electrode in the hypothalamus is shown in figures 4 *B* and 5.

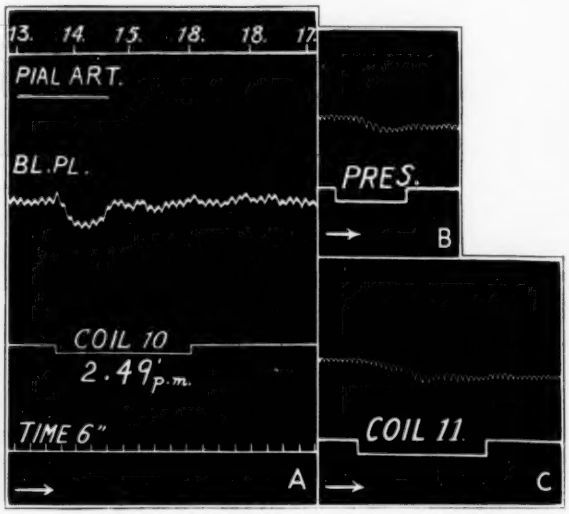

Fig. 1.—In figures 1, 2 and 3 the measurements of the pial artery are given in divisions of the scale of the microscope. The same way of recording is followed throughout. Each division of the scale is equivalent to 20 microns. *A* (experiment 8), stimulation of the ipsilateral tuber cinereum. *B* and *C* (experiment 16), stimulation of the contralateral tuber cinereum. The effect on the heart is shown. The pial artery dilated with both stimulations (*B*, mechanical pressure; *C*, electrical stimulation).

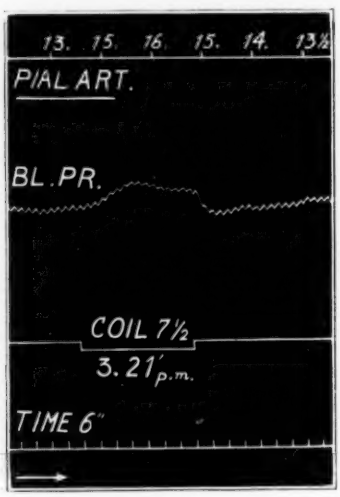

Fig. 2 (experiment 8).—Stimulation of the ipsilateral thalamus.

After this the electrode was inserted into the left hypothalamus and left there throughout the experiment. Its exact position can be seen in *A* of figure 4. With the insertion of the electrode the pial artery dilated to 16 divisions and maintained that diameter until the adrenalectomy.

In figure 3, *A* represents one of four stimulations of that region in the intact animal. Maximal dilatation of the pupils, erection of hair over the whole body, inhibition of the respiratory movements in the beginning of the stimulation followed by restlessness and acceleration of respiratory movements toward the end were seen on every occasion. In the beginning of the stimulation the pial artery dilated from 16 divisions to 17, this corresponding with the rise of blood pressure. After fifteen seconds of stimulation the artery began to constrict; at the end of stimulation it measured 13 divisions, and during the fall of the blood pressure it went down to 12; three minutes later it returned to 16 divisions. Shrinkage of the brain and pallor of the arterial wall accompanied the constriction of the pial

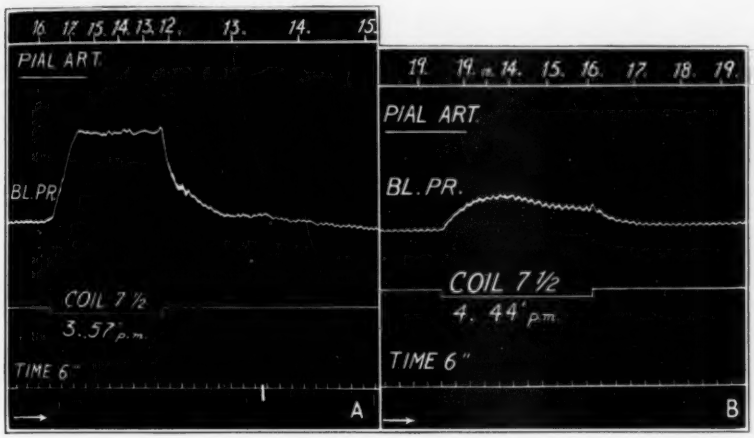

Fig. 3 (experiment 8).—*A*, stimulation of the contralateral hypothalamus before adrenalectomy; *B*, same stimulation repeated after adrenalectomy.

artery. Blood flow in the larger veins was not notably deferred; in some smaller veins the direction of the flow was reversed during the stimulation.

Toward the end of the experiment the adrenal glands were removed and four more stimulations carried out, figure 3*B* representing one of them. Maximal dilatation of the pupils accompanied these stimulations, too, but the erection of hair, restlessness and changes in respiratory movements were absent.

The pial artery, which after adrenalectomy had dilated to 19 divisions and stayed so until the end of the experiment, constricted during the stimulation to 14 divisions, this also being accompanied by a shrinkage of the brain. However, the constriction was not sustained throughout the stimulation and it began to weaken toward the end.

Note: A spontaneous dilatation of the pial artery after the insertion of the electrode and removal of adrenals is not typical and in most animals was not present.

In figure 4 four samples of the positions of the electrode in the hypothalamus are selected to give an idea of the most frontal, caudal, medial and lateral margins of the area from which constriction of the pial arteries was obtained.[66]

Figure 5 shows the sagittal section of a brain on which the extent of the operative procedure and the position of the electrode can be seen.

In table 1 are recorded all the experiments in which stimulations of the hypothalamus were carried out. This table shows the comparative frequency of occurrence of the different phenomena indicative of excitation of the sympathetic nervous system.

It will be seen from this table that dilatation of the pupils was the most constant phenomenon, but in two experiments, in spite of a good position of the electrode, even this effect was not marked. In these two experiments a slight transient dilatation of the pupils and rise of blood pressure were seen during the first three stimulations, but then disappeared. By changing the position of the electrode the effect

TABLE 1.—*Comparative Frequency of Different Phenomena Indicative of Excitation of the Sympathetic Nervous System* [66]

	Constriction of Pial Artery		Dilatation of Pupils		Rise in Blood Pressure		Erection of Hair		Salivation and Lacrimation		Micturition	
Experiments	Experiments	Per Cent	Experiments	Per Cent	Experiments	Per Cent	Experiments	Per Cent	Experiments	Per Cent	Experiments	Per Cent
47	35	74	47	100	44	94	23	57	11	23	4	8

could be obtained again on one or two stimulations. Apparently exhaustion of the stimulated region occurred rapidly, but the cause of this is not clear. With successive stimulations the animal seemed to fall into a state of deep sleep, bearing in that a resemblance to the condition noted by Hess.[67] Stimulation of the posterior parts of the hypothalamus was seen to produce micturition on several occasions. The position of the electrode in these cases corresponded well with the anatomic region of bladder control described by Lichtenstern [51] and represented in Greving's [68] diagram. As in many experiments the

66. In many experiments the electrode had to be reinserted two or three times before a constrictor response of the pial artery was obtained. The same is true of the other sympathetic manifestations, some of which were present in one position and the others in another. For this reason the table cannot illustrate the relative frequency of the phenomena observed; it shows merely the maximal figures of positive results throughout the work. If the total number of positions of the electrode in the hypothalamic region is calculated, the number of positive results most markedly decreases for the constriction of the pial artery. It decreases still more if the total number of stimulations is considered.

67. Hess, W. R.: Lancet **2**:1259, 1932; Le sommeil, Compt. rend. Soc. de biol. **107**:1333, 1931.

68. Greving, R., in Müller, L. R.: Lebensnerven und Lebenstriebe, ed. 3, Berlin, Julius Springer, 1931, p. 203.

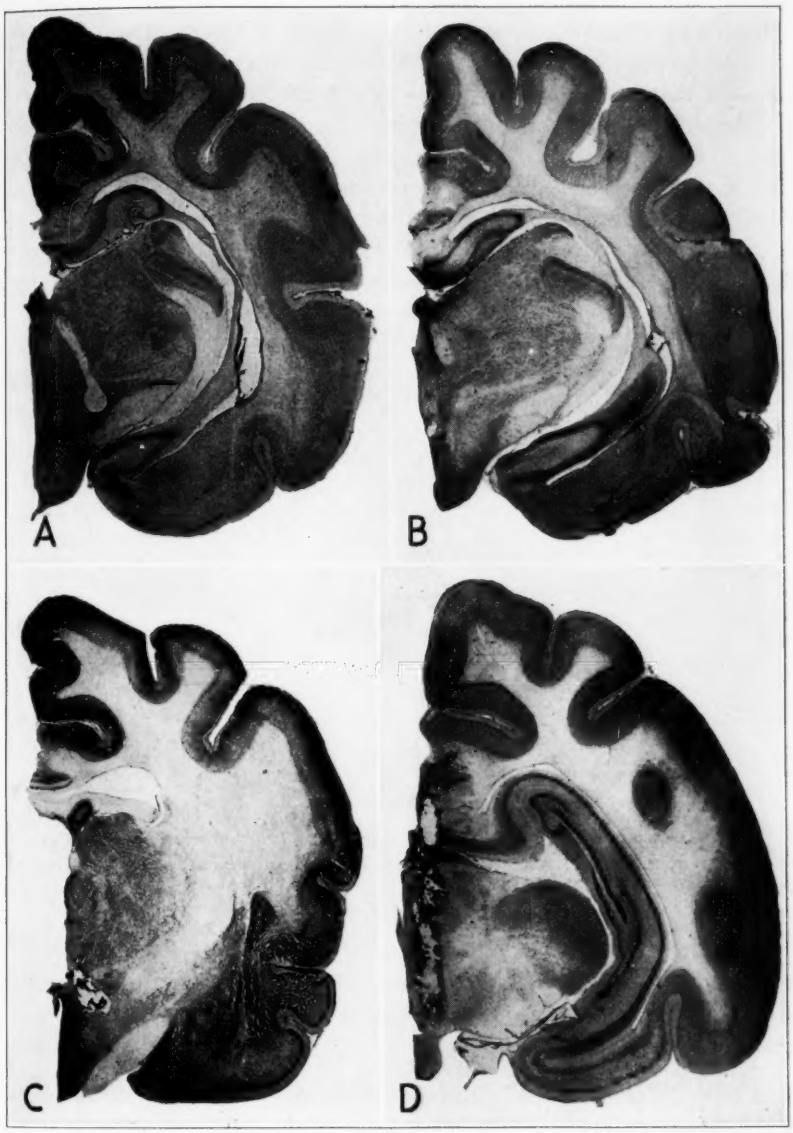

Fig. 4.—Four frontal sections of one hemisphere of the brain showing the positions of the electrode in the hypothalamus. Stimulation of these regions produced constriction of the pial arteries: *A* (experiment 9), one of the most lateral positions of the electrode; *B* (experiment 8), tip of the electrode close to the midline; *C* (experiment 17), one of the most anterior positions of the electrode; *D* (experiment 11), one of the posterior positions. (Compare this with figure 6.)

pleura was opened, no figure for the respiratory changes has been given. In one of seven most anterior positions of the electrode (fig. 6) sneezing-like movements were seen to come on during each stimulation, which apparently corresponded to the "spitting movements" of Ranson and Magoun [60c] and probably were altered in my experiments by the fixation of the head. Also loud cries, occurring mostly after the end of the stimulation, were occasionally noted. Flexion of one or both lower extremities was seen occasionally when the electrode was near the cerebral peduncle; an increase of tone also was noted with some of the most caudal positions of the electrode. Running movements arose frequently from any position except the frontal ones. Figures for these motor manifestations are not given as they have no significance

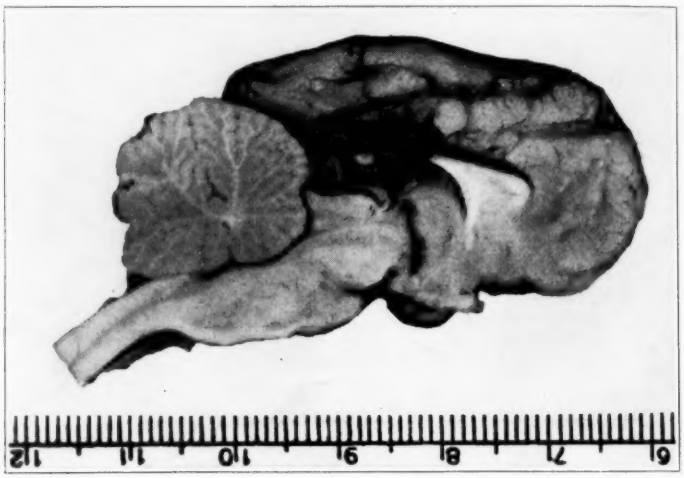

Fig. 5 (experiment 8).—Sagittal section of the brain showing the extent of the operative procedure and the macroscopic view of the position of the electrode. (Compare with fig. 4 *B*.)

in the absence of closer localization. Salivation and lacrimation were occasionally definite but not excessive. The rise of blood pressure and erection of hair will receive further attention in the analysis.

Analysis of the Constriction of the Pial Blood Vessels.—As the diminution in the diameter of the pial blood vessels in response to stimulation of the hypothalamus was mostly accompanied by a rise of the systemic blood pressure, it is considered to be of an active nature and regarded as true vasoconstriction. In some experiments effective stimulations could be repeated ten or eleven times, the constriction of the artery being so marked and its size between stimulations so constant as to leave no doubt as to the correctness of the observations.

In the majority of the experiments, however, this was not the case. Usually vasoconstriction was present during the first two or three stimulations and then tended to wear off, the artery becoming smaller after each successive stimulation and apparently failing to relax.

In some experiments, however, constrictions of the arteries appeared suddenly later in the experiment, being absent in the beginning. It could be seen on three or four stimulations and then disappeared as suddenly in some animals as it began in others. No definite cause of this variability of response could be detected, but it was noted in the course of the work that better responses of the pial arteries were obtained when some epinephrine hydrochloride was added to the saline or Ringer's solution used under the window. (A dilution of 1 : 400,000 to 1 : 800,000 was used.) It was also noted that sometimes the sympathetic responses to hypothalamic stimulation were increased for a long time by a single injection of histamine (1 mg. per cat).

The type of reaction varied, too; instead of pure vasoconstriction, in the majority of the experiments the initial diminution of the diameter of the artery was followed by dilatation as if overcome by the rise of blood pressure. On some occasions the artery maintained its size during the stimulation and constricted in the after-effect. In these cases occasionally ligation of the common carotid artery on the side of the skull window had a beneficial effect, making the constriction of the pial artery more regular and pronounced. Introduction of artificial respiration also seemed sometimes to stabilize the response to a certain degree. The latent period varied from seven or eight to from forty to fifty seconds. The after-effect sometimes disappeared as soon as from twenty to thirty seconds had elapsed, but was also seen to persist for two or three minutes or longer. It is true that in some animals the pupils also did not return to their initial size for longer periods of time.

The response of the pial arteries with the technic employed was bilateral. Vasoconstriction over the right hemisphere could be seen on stimulation of either hypothalamus, and in a control experiment in which two windows were applied the stimulation of one hypothalamic region was seen to cause vasoconstriction over both hemispheres.

On two occasions a complete cessation of circulation in the veins was seen to occur over the studied surface of the brain in response to stimulation. A description of these instances will now be given:

Experiment 11, Nov. 30, 1933: The cat weighed 1.7 Kg.; 0.3 cc. of dial per Kg. of body weight was injected intraperitoneally. The electrode was placed in the hypothalamus in the most dorsal position, close to the midline (fig. 6, *4*).

In five stimulations of one minute each, with the coil at 7.5 cm. and five minute intervals between stimulations, there were increased tone of the left lower leg, a rise of blood pressure and maximal dilatation of the pupils. The artery measured between 8 and 9 divisions, did not constrict during the stimulation, but did so

after it, measuring 7 or 6½ divisions, and returned to its original size in two or three minutes. There was no erection of hair. With successive stimulations the animal became restless, fits of panting occurred between stimulations, and the pupils would suddenly dilate by themselves, the pial artery swinging between 8 and 9.

At 3:42:30 p. m., the sixth stimulation was given. Maximal dilatation of the pupils was noted, with increase of tone in the left lower limb and patchy erection of hair over the whole body (for the first time!); the pial artery rapidly constricted from 9 to 7 divisions and became pale. After twenty-five seconds' stimulation all the veins in the field began rapidly to decrease in size and suddenly disappear and only a few clumps of stagnant red cells here and there indicated their previous position. The animal gave a jerk.

At 3:43 p. m., the stimulation was discontinued.

At 3:44 p. m., the animal recovered. The artery measured 9 divisions; the veins were visible again.

At 3:46:30 p. m., the circulation began to fail; blood cells were seen passing in the artery at a quick pace (not visible in normal conditions).

At 3:50 p. m., the animal died.

Experiment 17, Jan. 11, 1934: The cat weighed 1.9 Kg.; 0.3 cc. of dial per kilogram of body weight was injected intraperitoneally. The position of the electrode may be seen in figure 4 *C*.

At 2:30 p. m., the first stimulation was carried out, with the coil at 7.5 cm., for thirty-five seconds. There were dilatation of the pupils, erection of the hair and rigidity of the tail. The pial artery dilated from 9 divisions to 10 in ten seconds, and then rapidly constricted to 7 divisions. At thirty seconds the cat gave a few jerks and became very quiet; the veins rapidly diminished in size and at thirty-five seconds began to disappear. The stimulation was discontinued before complete emptying of the veins occurred. The animal recovered. The experiment continued. At no time were blood cells seen in the artery. The condition did not recur and could not be reproduced even with excessively strong currents. Erection of hair was seen on two other stimulations. The pial artery constricted on three more stimulations and then the effect disappeared.

The impression during the observations was that in both the described instances, at the time of stimulation, the venous return was greater than the amount of blood which was coming in and that this resulted in complete drainage of the superficial veins. That some circulation must have been preserved is concluded from the fact that the lumen of the artery was not occluded and that in spite of the emptying of the veins the blood flow in the artery during the stimulation was not retarded (blood cells not visible). Thus it must be assumed that the blood which was coming in through the arteries was drained by deeper channels, leaving the superficial veins temporarily empty.

In twelve experiments, even with repeated changes of the position of the electrode it was impossible to obtain any constriction of the pial arteries, though many other phenomena of sympathetic excitation were present and the position of the electrode corresponded to the ones in which active changes in size of the arteries were observed. In some of these experiments the size of the artery did not change during the

stimulations in spite of a rise of blood pressure; in others this was accompanied by an increase in the diameter of the artery.

In figure 6 thirty checked positions of the electrode in the hypothalamus are indicated in a diagrammatic way on five frontal sections. In all these positions of the electrode definite constriction of the pial artery was seen on three or more stimulations.

When these five groups of experiments were studied it became evident that in group 1 the constriction of the pial artery and pupillary

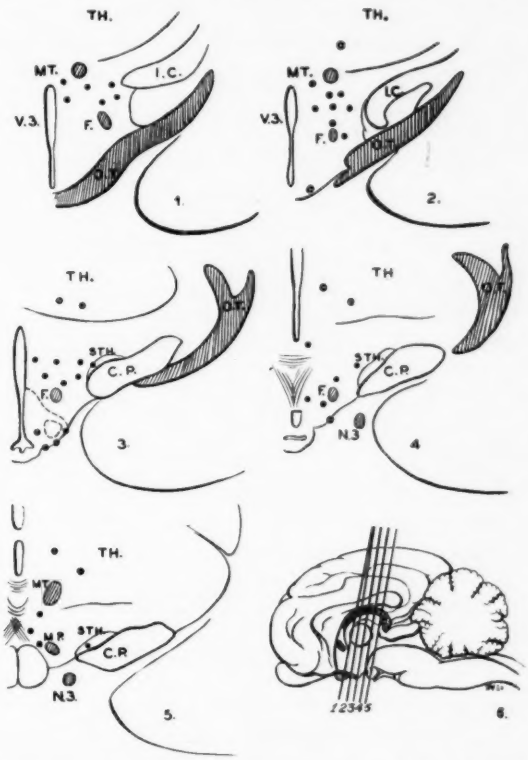

Fig. 6.—Diagrammatic record of the positions of the electrode in different experiments in which dilatation and constriction of the pial arteries were obtained. The small rings indicate regions in which stimulation resulted in an increase of the diameter of the pial blood vessels. The small black dots indicate regions in which stimulation resulted in a diminution of the size of the pial arteries. The abbreviations used are as follows: *TH*, thalamus; *O.T.*, optic tract; *v.3*, third ventricle; *I.C.*, internal capsule; *F.*, fornix; *MT*, mamillothalamic tract; *C.P.*, cerebral peduncle; *STH.*, subthalamic body; *N.3*, oculomotor nerve.

dilatation were often the only responses which were pronounced. In groups 2 and 3 also a purely constrictor response of the pial arteries predominated, but it was accompanied by a greater rise of blood pressure. In group 2 erection of hair was seen in three animals to occur only

over the upper part of the body. In groups 4 and 5 the rise of blood pressure, generalized erection of hair and respiratory changes were most pronounced. However, the response of the pial arteries varied, and constriction of these vessels was frequently preceded or followed by dilatation.

These relations are shown in table 2 and seem to suggest some degree of localization of the sympathetic functions in the dorsal part of the hypothalamus. This localization seems to lie in the anteroposterior direction, stimulation of the most anterior parts causing changes only in the head and upper part of the body, whereas stimulation of the posterior parts produced a diffuse, generalized effect. However, excep-

TABLE 2.—*Phenomena Indicative of Excitation of the Sympathetic Nervous System in Relation to Hypothalamic Region Stimulated*

	Change of Pial Artery in Response to Stimulation			Erection of Hair			
Group	Pure Constriction	Constriction with Dilatation	Dilatation of Pupils	Over Upper Part of Body	Generalized	Rise of Blood Pressure	Comment
Group 1 (6 experiments)	6	..	6	..	1	2 medium 3 slight 1 absent	No motor manifestations whatsoever
Group 2 (8 experiments)	7	1	8	3	4	7 medium and pronounced 1 slight	Motor phenomena in 3 experiments
Group 3 (7 experiments)	5	2	7	..	4	7 medium and pronounced	Some motor phenomena in all experiments
Group 4 (5 experiments)	2	3	5	..	4	5 pronounced	Motor phenomena only in 1 experiment (near cerebral peduncle)
Group 5 (4 experiments)	2	2	4	..	3	4 pronounced	Motor phenomena in 2 experiments

tions have been seen, and further work in this direction is necessary before a definite conclusion can be drawn. The different responses of the pial artery to stimulation of different regions of the dorsal part of the hypothalamus and the quantitative difference in the accompanying rise of blood pressure are shown in figure 7.

In five experiments the pleural cavity has been opened and artificial respiration introduced in order to exclude the influence of the respiratory changes taking place during the stimulation. As mentioned before, this procedure in some experiments appeared to facilitate and to stabilize the response of the pial arteries.

In seven experiments the adrenal glands were removed. In three animals the pial artery dilated after this procedure in spite of a fall of blood pressure (in two attempts artificial respiration was introduced at the beginning of the experiment).

As may be seen in figure 3, the constrictor response of the pial artery to stimulation of the hypothalamus was slightly reduced by the adrenalectomy, dilatation of the pupils persisted, the rise of the systemic blood pressure decreased considerably, and the pilo-erection disappeared. When the adrenals were removed in experiments in which no response of the pial artery was obtained prior to this operation the artery seemed even to have decreased in size, and the absence of the adrenals did not improve its response to hypothalamic stimulation.

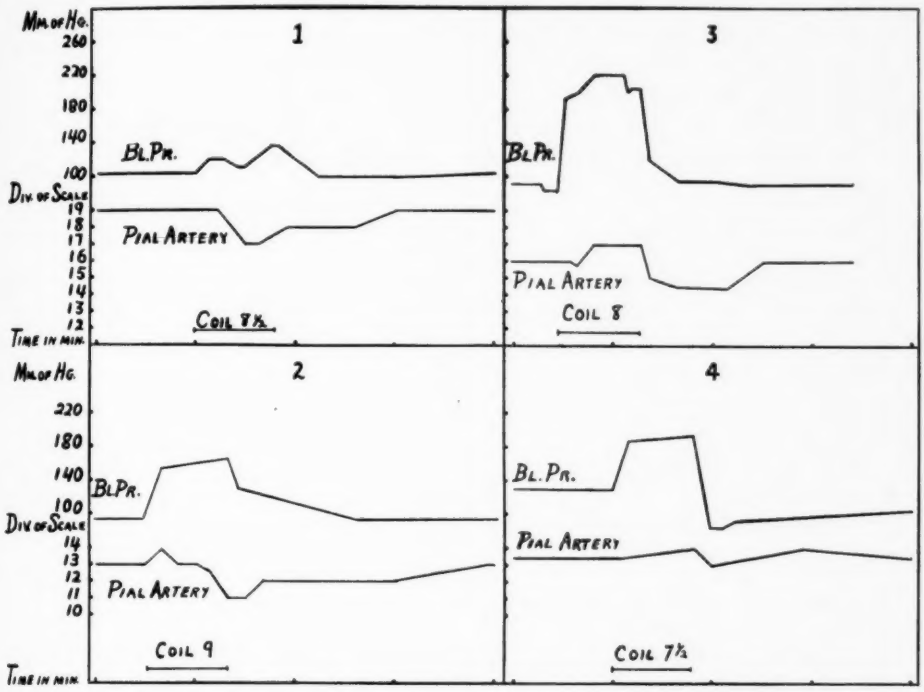

Fig. 7.—Examples of difference in the effect of stimulation of the hypothalamus. *1*, effect of stimulation of the most anterior part of the hypothalamic region from which the sympathetic responses were available (corresponds to diagram *1* of fig. 6). *2*, effect of stimulation of the middle part of this region (diagrams *2* and *3* of fig. 6). *3*, effect of stimulation of the most posterior part of this region (diagram *5* of fig. 6). Some increase of muscular tone during this stimulation may account partly for the extreme rise of blood pressure. *4*, a typical example of the experiments in which there was absence of response of the pial artery in spite of a very exact position of the electrode and presence of all the other manifestations of excitation of the sympathetic nervous system.

In two experiments constriction of the pial artery was seen after hypophysectomy. This was carried out from the base of the skull and, like adrenalectomy, did not improve the response of the pial artery in the experiments in which no response had been obtained prior to hypophysectomy.

In nine experiments constriction of the pial artery, retraction of the nictitating membrane and very slight dilatation of the pupils in response to stimulations of the hypothalamus were seen after section of the cervical sympathetic trunk in the neck and of the vertebral branch of the sympathetic nerve, after unilateral and bilateral removal of the inferior cervical sympathetic ganglion and after section of the spinal cord between the first and second cervical vertebrae.

These procedures occasionally were seen to increase the size of the artery and tended to reduce the amount of constriction but did not abolish it, and even after bilateral removal of the cervical sympathetic ganglia and complete section of the spinal cord in one animal slight dilatation of the pupils and constriction of the pial artery were seen quite definitely with repeated stimulations of the hypothalamus.

Two examples may be quoted:

Experiment 9, Nov. 23, 1933: A cat was given 0.3 cc. of dial per kilogram of body weight by intraperitoneal injection. The electrode was at the anterior part of the corpus Luysi. Stimulations were carried out with the coil at 8 cm. for one minute each. Readings of the artery were taken at one minute intervals, and those for the periods of stimulation are italicized.

At from 4:11 to 4:19 p. m., the arterial measurements in divisions were 15, 15, *12½*, 12½, 13, 13½, 14½, 15. The percentage of constriction was 16.6.

At 4:20 p. m., the cervical sympathetic trunk was cut on the side of the window.

At from 4:21 to 4:27 p. m., the arterial measurements were 15, *13¾*, 13¾, 13¾, 14, 14½. The percentage of constriction was 8.1.

Experiment 15, Dec. 28, 1933: A cat was given 0.3 cc. of dial per kilogram of body weight by intraperitoneal injection. The electrode was in the same position as in experiment 9, only 2 mm. medially. Stimulation was carried out with the coil at 7.5 cm. for thirty seconds and thirty-five seconds. Readings of the artery were taken at thirty second intervals, and those during the period of stimulation are italicized.

At 4:26 p. m., both inferior cervical sympathetic ganglia were removed.

At from 4:32 to 4:38 p. m., the arterial measurements were 9, 9, *7½*, 9, 9, 9, *8*, 9, 9, 9, *8*, 9, 9, 9. The percentage of constriction was 11.

At from 4:40 to 4:49 p. m., the spinal cord was sectioned between the first and second cervical vertebrae.

At from 4:38 to 4:43 p. m., the arterial measurements were 9, 9, *8*, 9, 9, 9, *8*, 9, 9, 9. The percentage of constriction was 11.

Higher transsections—through the middle of the rhombencephalon—seemed to abolish these residual responses.

These sections were carried out through the cerebellum and extended into the lower third of the pons, leaving the mesencephalon and oculomotor nerves intact.

Both the residual ocular responses and constriction of the pial artery were abolished by this procedure, and further stimulations

of the hypothalamus were ineffective. Stronger currents caused even a slight constriction of the pupils. Throughout this experiment the position of the electrode was not changed.

Analysis of the Dilatation of the Pial Arteries.—Dorsal Hypothalamus—Passive Dilatation: As may be seen from the data presented, stimulation of the dorsal region of the hypothalamus on many occasions produced, instead of a constrictor response, dilatation of the pial arteries. A marked rise of blood pressure occurred with both these types of reaction of the pial vessels. Dilatation of the pial vessels was never obtained without it, and when present it was not pronounced and disappeared with the restoration of the normal blood pressure level. It seems justifiable to assume, therefore, that the true response of the pial arteries to stimulations of the dorsal hypothalamic region is constriction. The dilatation, when seen, was probably secondary to the rise of blood pressure and occurred only in the absence of an active constrictor response of the pial arteries.

Tuber Cinereum—Active Dilatation: A second region stimulation of which resulted in an increase of the diameter of the pial arteries was the ventral and ventrolateral portions of the tuber cinereum. Dilatation of the pial arteries in response to stimulation of the tuber was obtained in six experiments. As may be seen in figure 1, stimulation of this region produced a slight fall of blood pressure and in several experiments slowing of the heart and a pronounced increase in the diameter of the pial artery. This dilatation began soon after the onset of the stimulation and gradually reached its peak. After the end of the stimulation the artery soon resumed its initial size, and the stimulation could be repeated many times during the same experiment with constant results. In these experiments unilateral and bilateral constriction of pupils was noted, but this effect received no special attention. It has been pointed out lately by Ranson and Magoun [62c] that stimulation of the optic tract, in the vicinity of which the electrode in my experiments was often placed, may result in bilateral constriction of the pupils, whereas unilateral constriction can be attributed to the closeness of the oculomotor nerve, which makes the interpretation difficult. The fall of blood pressure, however, and the change of heart rate (studied in detail by Beattie [59]) which in my experiments accompanied the dilatation of the pial artery seem to indicate that the dilatation is active and so is one of the specific effects of tuber stimulation.

Thalamus: The third region from which dilatation of the pial arteries was elicited was the thalamus. As seen in figure 2, the rise of blood pressure was insignificant and the enlargement of the pupils was moderate, yet dilatation of the pial arteries was pronounced.

Sachs [46] attributed the autonomic phenomena seen on stimulation of the thalamus to excitation of sensory pathways, and later work seemed

to justify this conception. As mentioned before, however, many investigators have succeeded in observing constriction of the pial arteries on stimulation of sensory nerves, and yet on stimulation of the thalamus I noted pronounced dilatation. The following experiment was then carried out: In an animal in which hypothalamic stimulation produced repeatedly good constriction of the pial artery, the sciatic nerve was dissected and its central end stimulated. The pial artery responded by constriction. Two electrodes were then placed in each thalamus. Stimulation of either of them caused the artery to dilate. Repeated stimulation of the hypothalamus and sciatic nerve again caused constriction of the pial artery. This experiment was repeated on another occasion with similar results.

A brief protocol will serve as an illustration:

Experiment *22*, Feb. *22*, 1934: A male cat weighing 3 Kg. was given 0.3 cc. of dial per kilogram of body weight intraperitoneally. The electrode was in the right hypothalamus; the window was on the side of stimulation. Readings of the pial artery were taken at one minute intervals. Stimulations, lasting one minute each, were performed with the coil set at 8 cm. and repeated nine times. The readings at periods of stimulation are italicized.

The arterial measurements for a sample stimulation of the hypothalamus were 9, 9, *7*, 7, 8, 9, 9. For stimulation of the right sciatic nerve (repeated four times) the arterial measurements were 9, 9, *7½*, 8½, 9, 9, 9, 8½, 8½, *7*, 8, 8, 8, 8. For stimulation of the thalamus, three times right, twice left, the arterial measurements were 8, 8, *11*, 8, 8, 8, 8, *11*, 8, 8, 8, 8, *11*, 8, 8, 8. For stimulation of the hypothalamus repeated, the measurements were 8, 8, *6*, 7, 8, 8, 8, *6*, 7, 8, 8.

In all, six experiments which included stimulation of the sciatic nerve were performed. In three animals stimulation of this nerve caused constriction of the pial artery, this effect persisting after adrenalectomy, removal of the hypophysis and extirpation of the inferior cervical sympathetic ganglion on the side of the skull window. In one of them a single stimulation of the sciatic nerve caused slight dilatation of the artery, but if a minute later a second stimulation was applied the artery responded by constriction, and this sequence of events persisted throughout the experiment. In three animals dilatation of the pial artery accompanied stimulation of the sciatic nerve.

No adequate explanation of these experiments can be offered at present, but they seem to demonstrate that the response of the pial vessels obtained on stimulation of the thalamus is not always identical with that produced by stimulation of the sensory nerves.

COMMENT

The experiments presented demonstrate, in my opinion, that by stimulation of the hypothalamus it is possible to obtain a constriction of the pial arteries with other phenomena of excitation of the sym-

pathetic nervous system. This effect was proved not to depend on changes in respiration and not to be counteracted by a considerable rise of blood pressure; nor was it abolished by removal of the adrenal glands and the hypophysis cerebri. This observation is in agreement with the findings of Karplus and Kreidl [47a] for vasoconstriction in other regions of the body. The effect was diminished but present after section of the cervical sympathetic trunk, removal of the inferior sympathetic ganglia and complete section of the spinal cord below the medulla, but disappeared with transsections through the lower third of the pons. The residual effect observed on stimulation of the hypothalamus after section of the cervical sympathetic nerve included, besides constriction of the pial arteries, slight dilatation of the pupils and retraction of the nictitating membrane.

Karplus and Kreidl,[47a] using minimal currents, did not see dilatation of the pupils on hypothalamic stimulation after section of the cervical sympathetic trunk, but did see it as a reflex effect of stimulation of sensory nerves after section of the sympathetic nerve. They have explained this dilatation as a result of inhibition of the tone of the oculomotor nerve, on the basis of reciprocal innervation.

It is conceivable that the minimal stimulus used by Karplus and Kreidl [47a] in hypothalamic stimulation was insufficient to produce a response after the main bulk of sympathetic fibers was removed, but that by the application of slightly stronger currents—required in my experiments for the production of the constriction of the pial arteries —it still could be elicited. Different experimental conditions, particularly the anesthesia, may also have to be considered. Their explanation of the mechanism of this residual effect is applicable in my experiments also.

However, both Huber [16] and Penfield,[21] on the basis of histologic studies on sympathectomized animals, came to the conclusion that the origin of intracranial vascular nerves is not altogether in the sympathetic ganglia. It is possible to conceive that some aberrant nervous pathways join the intracranial blood vessels and reach the eye without descending into the spinal cord.

As may be seen from the diagram presented, the anatomic location of the hypothalamic region from which the effects of sympathetic excitation were obtained corresponds closely with the description given by Karplus and Kreidl [47a] and the findings of Ranson and his co-workers.[60]

It has been noted also that with the electrode in the most rostral positions the rise of blood pressure was absent or insignificant; erection of hair in five experiments was seen only over the upper half of the body, and on one occasion the effects were restricted to dilatation of the pupils and constriction of the pial arteries. With the electrode in the midhypothalamic region all the sympathetic phenomena were more pronounced and erection of hair when seen occurred over the

whole body. With the electrode in the most posterior positions the rise of blood pressure seemed to counteract the constriction of the pial vessels, which became prominent only in the after-effect. These observations have created the impression that in the hypothalamus there exists some sort of localization of function, presumably in the antero-posterior direction.

In the animal studied—the cat—the effect of hypothalamic stimulation was bilateral. This fact received due attention from Karplus and Kreidl,[47a] who concluded that part of the sympathetic fibers must cross high in the spinal cord. It is interesting that after complete section of the spinal cord below the medulla the residual effect of hypothalamic stimulation in my experiments was still strictly bilateral, though with the present technic the possibility of spread of stimulating current from one hypothalamus to the other side is not excluded.

Stimulation of the ventral hypothalamic region, particularly the "tuber nuclei" of Beattie,[59] caused dilatation of the pial arteries. As this effect was accompanied by a fall of blood pressure and slowing of the heart, it is considered to be of an active nature, which agrees with the findings of Beattie.[59]

The fact that stimulation of sensory nerves causes constriction of the pial vessels in some animals and dilatation in others has no explanation at present. Most unexpected, too, was the finding that even when stimulation of the sciatic nerve caused constriction of the pial arteries, stimulation of the thalamus still produced dilatation of these vessels, the rise of blood pressure and other phenomena being approximately the same.

In order to avoid a wrong impression as to the constancy of the results obtained the variability of the response of the pial blood vessels to central stimulation should again be mentioned. In approximately one quarter of the experiments no responses were obtained, whereas a constant effect suitable for further analysis was seen only in one out of every four or five experiments. In spite of every attempt to find the cause of this variability, so far it has remained undetermined, and though the position of the electrode was probably responsible for some failures it cannot serve to account for all of them. This unreliability of the effect of stimulation rendered analysis of the reaction of the pial vessels most difficult.

On account of this no attempt was made in the present investigation to study the intimate nature of the observed reactions and of the peripheral paths by which impulses might have reached the pial blood vessels.

The possibility of spread of current was carefully excluded. The electrode was so insulated that only the cross-section of the wires was free. On lowering the electrode with a continuous stimulation, a silent

area between the thalamus and hypothalamus was definitely observed, as judged by the effect on the pupils. By lowering the electrode into the ventral parts of the hypothalamus, the dilator response of the pupils, erection of hair and rapid breathing were immediately abolished, showing that the stimulation was very localized. This is true also of the constriction of the pial vessels, which was explored systematically and found to be absent on lowering or raising the electrode, reappearing when the electrode struck the dorsal parts of the hypothalamus.

Direct stimulation of the internal carotid artery or the proximal end of the middle cerebral artery caused only local circular constriction of these arteries at the stimulated point, as observed by Cushing,[69] but did not alter notably the diameter of the distal branches of these arteries situated over the hemisphere, even when they were studied under the microscope.

These and other considerations convince me that the responses of the pial vessels observed are the results of stimulation of the localized regions of the central nervous system and are not due to any complicating factors. The prolonged response of the pial arteries which appeared only after a longer latent period than the rise of blood pressure I believe, with other workers, to be characteristic of these vessels.

On no occasion during the present experiments was the constriction of the pial vessels followed by an epileptic discharge, and only in two instances in which complete emptying of the veins occurred were abrupt jerks seen. As the animals were under considerable sedative doses of dial, however, no conclusions can be drawn from this observation.

On the other hand, on several occasions progressive enlargement of the pupils and reappearance or persistence of other effects of sympathetic excitation after removal of the stimulation were seen, which almost suggested an epileptic march of autonomic manifestations. The possibility of such an occurrence of autonomic epileptic discharges has been demonstrated by Penfield [70] in a clinical case in which a movable tumor in the third ventricle produced attacks limited to autonomic phenomena.

SUMMARY AND CONCLUSIONS

1. In cats electrical stimulation of the dorsal or "posterior" region of the hypothalamus, situated between the cerebral peduncles and the third ventricle, may produce a constriction of the pial blood vessels, this response being bilateral. Other effects of excitation of the sympa-

69. Cushing, H.: Some Experimental and Clinical Observations Concerning States of Increased Intracranial Pressure, Am. J. M. Sc. **124**:376, 1902.

70. Penfield, W.: Diencephalic Autonomic Epilepsy, Arch. Neurol. & Psychiat. **22**:358 (Aug.) 1929.

thetic nervous system were also seen on stimulation of this region, such as dilatation of the pupils, retraction of the nictitating membranes, widening of the palpebral fissures, rise of blood pressure, erection of hair, hyperpnea, salivation, lacrimation, cries and urination.

2. The constrictor response of the pial arteries is not a constant effect, being absent on many occasions. When present it comes on more slowly than the rise of the systemic blood pressure, considerably outlasts it after the end of the stimulation and requires for its demonstration the application of stronger currents than any other effect obtained from that region.

3. The constriction of the pial blood vessels seems to be diminished but is not abolished by section of the cervical sympathetic trunk, by removal of the inferior cervical sympathetic ganglia or by complete section of the spinal cord below the medulla, this being true also of the ocular responses. These residual responses disappear after transsection through the lower third of the pons.

4. The constriction of the pial blood vessels and the rise of the systemic blood pressure are not dependent on changes in respiration and can be obtained after bilateral removal of the adrenals and after hypophysectomy. They have been seen to occur also in the absence of any notable motor manifestations.

5. Stimulation of the most ventral region of the hypothalamus, namely the ventral and ventrolateral parts of the tuber cinereum, causes dilatation of the pial arteries. This response is also bilateral and is accompanied by a lowering of the systemic blood pressure and slight inhibition of the rate of the contractions of the heart.

6. Stimulation of the central end of the sciatic nerve may produce reflexly either dilatation or constriction of the pial arteries, the response varying from experiment to experiment.

Stimulation of the thalamus causes dilatation of the pial vessels.

In both instances the effect on the pial blood vessels is accompanied by a slight rise of blood pressure, moderate dilatation of the pupils and hyperpnea.

In conclusion it seems justifiable to state that stimulation of different hypothalamic regions in cats may cause active constriction and dilatation of the pial blood vessels.

THE EXPERIENCE OF THE BODY-SELF IN SCHIZOPHRENIA

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One finds in the literature an occasional remark that the seemingly bizarre ideas about one's body which are common in certain forms of schizophrenia may have some sensory basis, but as far as I know the problem has never been investigated. In a previous paper [1] some of the somatic delusions of a schizophrenic patient were analyzed, and an attempt was made to show that such delusions had a definite perceptual basis consisting of tactile and kinesthetic phenomena which, under certain conditions, can be elicited in normal persons as well. Though only a single subject was analyzed, the opinion was expressed that the symptoms and the mechanism involved are probably not rare phenomena. Since then, new material has accumulated, and it is now possible to deal with the problem in a more comprehensive fashion.

Since many of the symptoms to be analyzed in this paper are related to perceptual phenomena in the field of muscle sensation, a discussion of muscle sensations observed under physiologic conditions will be given first. This is necessary because the view on muscle sensations reported here deviates in many respects from current theories, and part of it will be reported for the first time in this paper. In the second part of the paper, a group of somatic "delusions" are analyzed, and it is demonstrated that they have a definite perceptual basis in kinesthetic sensations. In the third part, the disturbances of the postural model of the body in schizophrenic patients are discussed, and it is proved that although these phenomena are to a large extent dependent on muscle sensations, they also probably involve other factors. The latter are then discussed in both the clinical and the neuropathologic aspects.

I. NEUROPHYSIOLOGIC CONSIDERATIONS OF MUSCLE SENSATIONS

The Muscle Sense Under Physiologic Conditions.—In earlier theories it was assumed that the intensity of weight perception is directly proportional to the strength of muscle contraction employed in lifting or balancing a weight. That is, the stronger the contraction of the muscle, the heavier the object appears. Later, however, various phenomena were observed which seemed to contradict the assumption

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1. Angyal, A.: The Perceptual Basis of Somatic Delusions in a Case of Schizophrenia, Arch. Neurol. & Psychiat. **34**:270 (Aug.) 1935.

of such a simple relation between the amount of subjectively perceived weight and the strength of contraction. Observations of the type of Charpentier's illusion are directly contrary to such an assumption. Charpentier's illusion arises when one compares two objects which are objectively equal in weight but which, judging from their visual appearance, e. g., difference in volume or material, seem to have different weights. Under such conditions, by lifting one perceives the object of heavy appearance as light and vice versa. Muscles are innervated for the lifting of an object according to the expected weight. In such instances, therefore, an object lifted with a strong contraction of the muscles is perceived as light, and the same objective weight lifted with a weaker contraction is perceived as heavy.

Thus, it seems that there is no direct proportionality between the strength of the contraction of the muscles and the perceived weight. On the contrary, the strength of the contraction and the amount of perceived weight seem to be inversely proportional to each other, as was assumed by Ponzo and me.[2] According to our view, the intensity of perception of weight depends neither on the amount of physical weight alone nor on the strength of muscle contraction employed in lifting an object alone but on the interrelation of the strength of the muscle contraction and the physical stimulus. The intensity of the weight perception is directly proportional to the physical weight and inversely proportional to the strength of the contraction of the muscles. If the physical weight remains constant, the object will appear as subjectively lighter the greater the muscle tension with which it is lifted.

It is assumed that it is not the contraction of the muscle which is perceived as weight but the impediment which the object through its physical weight offers to the contraction of the muscle.[3] The impediment which is meant here is defined not by the physical weight of the object but by the amount of stretch (measured in length) which this weight is able to produce in the muscles in question. By the term stretch, I mean the amount of elongation which a given weight is able to produce in a muscle, or in a group of muscles, of a given tonus. The same objective weight produces less elongation when the muscle has a strong tonus than when it has a low tonus. There is, therefore, in the former instance a smaller stretch than in the latter instance. The stretching power of the weight on the muscle is the correlate of the intensity of weight perception. In other words, this hypothesis assumes that the amount of subjectively perceived weight is directly proportional

2. Ponzo, M., and Angyal, A.: Zur Systematik der Gewichtsempfindungen, Arch. f. d. ges. Psychol. **88**:629, 1933.

3. For the interpretation of the inverse relation between the intensity of weight perception and the degree of muscle tension and for the extension of the theory which here follows, I alone assume responsibility.

to the amount of impediment of the contraction of the muscle or to the stretch of the muscle measured in units of length.

Attention should be paid to the fact that in the proposed hypothesis not the actual elongation of the muscle is assumed to be the correlate of the intensity of weight perception but the impediment of the contraction of the muscle measured in units of length. In fact, when one lifts an object, the muscle concerned does not lengthen but becomes shorter. In such a condition two opposite forces are operating (figure): the active contraction (*a*), which tends to shorten the muscle, and the weight, which tends to stretch it. Force *a* being the greater, the result will be a shortening of the muscle (*c*). But the impediment of the contraction of the muscle (*b*) caused by the weight in such circumstances can be well expressed in units of length.

Stretches of equal length on the muscles are perceived as subjectively equal weights. This explains well the fact that the same object lifted with a forceful contraction of the muscle appears lighter than if it is lifted with a weaker contraction. In the former instance the weight produces less stretch (measured in units of length) in the muscle than in the latter instance.

Diagram of the forces involved in the lifting of a weight. The active contraction (*a*) tends to shorten the muscle, while the weight tends to lengthen it. Force *a* being the greater, the result will be a shortening of the muscle (*c*). The impediment of the contraction (*b*) is caused by the weight in such circumstances.

The stretch of the muscle must be of a certain quantity in order that it may be perceived as weight. This minimal stretch corresponds to the threshold of sensitivity. A given physical weight which is over the threshold for a moderately contracted muscle falls under the threshold if the strength of contraction is increased.

According to the hypothesis presented here, all the factors which have an influence on the capacity for stretch, e. g., the size of the muscle and its physiologic conditions, must influence the intensity of weight perception. Pickler [4] called attention to the fact, and Panzel [5] demonstrated experimentally, that the weight of a load lifted with one finger is definitely overestimated when it is compared with that of a load of objectively equal weight lifted with the biceps muscle. To a person in a state of asthenia, weights appear heavier. Panzel [5] also showed that in cases of atrophia progressiva musculorum the affected side

4. Pickler, J.: Die Anpassungstheorie der Empfindungen, Leipzig, J. A. Barth, 1920.

5. Panzel, A.: Untersuchungen über das Vergleichen von Gewichten bei Gesunden und Kranken, Deutsche Ztschr. f. Nervenh. **87**:161, 1925.

strongly overestimates weight. All these and similar conditions can be explained easily if one regards the impediment of contraction of the muscle expressed in units of length as the correlate of the intensity of weight perception.

When an object is lifted there is an interplay between two factors: the contraction of the muscle due to a voluntary innervation and the external resistance on which the contracting muscle acts. This resistance is represented usually by the weight of the object alone; but if an involuntary contraction is also present when one lifts an object, this involuntary contraction also acts as an external resistance. Therefore, an object appears heavier when there is an involuntary contraction in the antagonistic muscle group, because the involuntary contraction in the antagonists plus the physical weight of the object exercises a greater stretch on the agonists than would the weight of the object alone. Correspondingly, when besides the voluntary contraction there is an involuntary contraction in the agonists, the object will appear lighter than in the absence of such contraction.

These facts were clearly demonstrated in Matthaei's [6] studies. He demonstrated experimentally that objects appear lighter when the muscles which lift the weight are in a state of catatonus. Catatonus, or phenomenon of Salmon and Kohnstamm,[7] is an involuntary postcontraction. This can be elicited by the exertion of a considerable force for about thirty seconds against an external resistance. After the voluntary contraction is relieved and the external resistance is removed, an involuntary after-contraction of the same muscle group tends to change the position of the limb in the direction of the original contraction. The fact that an object appears lighter when the group of muscles lifting the weight are in a state of catatonus makes it seem, according to the view of Matthaei, "as if only the voluntarily elicited muscle tension from which the brain obtains a sensation through the organs of the muscle-sense is considered by the judgment of weights, and in some way the effect brought about involuntarily through the after-contraction is not taken into consideration, . . . for the judgment of weight is determined . . . only by the voluntarily elicited part of the muscle tension."

I agree with Matthaei that for the explanation of this phenomenon it is necessary to distinguish between the voluntary and the involuntary component of contraction of a muscle. But while Matthaei assumed that the voluntary part of the contraction is the physiologic correlate

6. Matthaei, R.: Nachbewegungen beim Menschen, Arch. f. d. ges. Physiol. **204**:587, 1924.

7. This catatonus is often called the phenomenon of Kohnstamm. But Salmon (Salmon, A.: Di un curioso fenomeno di automatismo che si osserva dopo gli sforzi muscolari nei soggetti sani, Quaderni di psichiat. **1**:57, 1914) described it a year before Kohnstamm.

of the weight perception, the theory advanced here puts the effectiveness of the impediment of the voluntary contraction of the muscle, measured in units of length, in relation to the quantity of the subjectively perceived weight. The external force which causes the impediment of the contraction of the muscle is represented in Matthaei's experiment by the physical weight of the object and the catatonus. The catatonus, in Matthaei's experiments, having the same direction as the voluntary contraction of the muscle, the total external resistance against the voluntary contraction equals the physical weight minus the catatonus. Consequently, the object will appear lighter than it would in the absence of catatonus. If one induces the catatonus in the antagonistic muscle group and lifts a weight, the resistance equals the physical weight plus catatonus, and therefore the weight will appear heavier.

This interpretation is in agreement with the view of Schilder [8] with regard to the perception of the weight of one's own body. Schilder stated: "When there is a pull of the tone in a special direction, the amount of this pull is added to or subtracted from the gravity of the body." As an example, Schilder referred to the experiments of Fischer [9] and Wodak, who demonstrated that if one induces a difference in tonus between the two sides of the body by irritation of the vestibular apparatus with cold water while the two arms are stretched forward horizontally, one arm will rise and seem lighter and the other will fall and seem heavier. The conditions are essentially identical with those in Matthaei's experiments, both the catatonus and the tonus of vestibular origin being involuntary and accounted for as "external" impediments of the voluntary contraction.[10]

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8. Schilder, P.: The Vestibular Apparatus in Neurosis and Psychosis, J. Nerv. & Ment. Dis. **78**:1 (July); 137 (Aug.) 1933.

9. Fischer, M. H.: Die Regulationsfunktionen des menschlichen Labyrinthes und die Zusammenhänge mit verwandten Funktionen, Ergebn. d. Physiol. **27**: 209, 1928.

10. Schilder gave another example for the additive combination of the physical weight and tonus. He stated: "Spontaneously, a rising extremity is lighter and an extremity sinking down is heavier." [8] This observation is correct, but I am of the opinion that the mechanism involved in this phenomenon is different from that observed in the experiment of Fischer and Wodak. The arms are usually raised with slightly excessive tonus, whereas when the arm is dropped the tonus is diminished, since it is pulled down partly through the physical weight. The tonus of the rising arm is greater than that of the sinking arm. It has already been pointed out that the objective weight appears lighter, the greater the voluntary muscle tension. If one voluntarily raises the arm with a small tonus and puts it down with an energetic movement, the arm when rising will appear heavier and when sinking lighter. It may be mentioned that in an earlier paper Schilder (Schilder, P.: Notiz über Gewichtsschätzungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:676, 1927) also assumed, in agreement with Goldstein, that only certain types of tonus become summatively combined with the physical weight. My opinion is that only the involuntary tonus acts as an external resistance.

After these general considerations, I wish to report some kinesthetic phenomena, which were observed first by Ponzo [11] in normal persons, since these phenomena are closely related to certain somatic delusions of schizophrenic persons which are to be discussed in this paper. Ponzo used in his experiments a simple apparatus consisting of two receptacles connected by a tube. The subject standing with closed eyes holds one of the receptacles, filled with water (about 300 Gm.), in his hand with the arm stretched directly up. The experimenter can drain the water noiselessly from the receptacle by lowering the second receptacle and opening a stopcock. In such conditions the subject usually does not notice that the receptacle has gradually lost weight, though the loss of weight far exceeds the threshold of sensibility. The first change of which he becomes aware, and this usually happens only when the greater part of the water is drained off, is an impression that the receptacle has all at once lost its entire weight, giving a peculiar sensation of lightness. This sensation of lightness, as Ponzo and Angyal pointed out,[2] is not identical either with a slight degree of heaviness or with the absence of the sensation of weight but is a sensory quality sui generis.[12]

The emergence of this quality of lightness in Ponzo's experiments can be explained in the terms of my hypothesis. In Ponzo's experiments the diminution of weight takes place without the knowledge of the subject, who therefore tends to maintain his muscles in the initial degree of contraction. As the receptacle is gradually emptied, the weight sinks under the threshold for the given tension of the muscles, or, in other words, the weight cannot produce in the contracted muscle the minimal stretch which is the physiologic correlate of the threshold of sensitivity. In the meantime, an involuntary contraction (the catatonus of Salmon and Kohnstamm) occurs, which has the same direction as the voluntary contraction of the agonists. The involuntary contraction is physiologically accounted for as an external force. But while a weight tends to lengthen the contracting muscle, the catatonus tends to shorten it. This antagonism of the physiologic processes is reflected also on the psychologic side. An external force which tends to lengthen the contracting muscle is experienced as heaviness, and an "external" (involuntary) force which tends to shorten it gives the specific sensory quality of lightness.

If during the previously described experimental situation of Ponzo the attention is directed to the impressions on one's own body and not

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11. Ponzo, M.: Phénomènes d'annulation perceptive avec des "stimulus" subliminaries, Kwartalnik Psychol. **1**:3, 1930.

12. Fechner (Fechner, G. T.: Ueber die Kontrastempfindung, Ber. u. d. Verhandl. d. k. Sächs. Gesellsch. d. Wissensch. z. Leipzig, Math.-Phys. Kl. **12**:76, 1830) knew about this specific quality of lightness, which "is not to be confused with absence or unconsciousness of the sensation."

to the receptacle, one experiences peculiar deformations of the postural model of the body. The deformations are dependent on the position of the part of the body which supports the weight: If the arm is stretched horizontally, it seems to rise above the horizontal when the weight is lessened; if the arm is stretched up, it seems to elongate itself. If the weight is placed on the eyeball, one has a clear impression when the weight diminishes of the eye protruding several inches out of the face. If the weight is placed on the head of the subject, he feels as though he were becoming taller, growing into the air, as the weight diminishes. If instead of diminishing one increases the weight resting on the head, some subjects feel that the body is becoming shorter. But this impression is never so marked as the experience of elongation of the body.

Some subjects experience not so much a sense of deformation of the body as of a light, airy substance passing through the limb and emanating from the body, or they have the impression of a light fantom limb reaching out from the body in the direction of the pull of the muscle tonus.

II. SOMATIC DELUSIONS BASED ON MUSCLE SENSATIONS

The Loss of Ego-Reference of Experiences, with Special Regard to Kinesthetic Experiences.—Observations on a single subject were chosen for the report. The phenomena to be discussed are marked, and the patient is able to give detailed information about his experiences. Besides this, there is the great advantage that the patient, presenting other problems besides those which will be considered here, was studied intensively for six months in daily interviews; hence a considerable mass of information has been collected about the personality, psychosis and past history. All details of the history of the case which are not essential for an understanding of the phenomena to be discussed in this paper will be omitted, and such data as are related to the present problem will be given at the proper place. However, one group of symptoms of this patient, which reveal profound disturbances of self-awareness, should be considered at this juncture.

In a previous paper[1] the opinion was expressed that some of the seemingly bizarre somatic complaints of patients with schizophrenia have their basis in a profoundly disturbed self-awareness. Disturbances of self-awareness provide a favorable condition for the appearance of some unusual perceptual phenomena which otherwise are observable only under special conditions set by the experimenter.

In my patient, as in many schizophrenic patients, the basic differentiation between the ego and the external world is grossly impaired. Parts of the patient's body and of his mental and physical activities are excluded from self-awareness, are not experienced as belonging to his ego. The patient complains that the jaw he has is not his jaw, "it is only set in." He complains that his arm feels "life-

less," does not belong to him; that he has "no real skull but only a wooden frame"; that his teeth are "false," etc. Some of the thoughts he has are not his thoughts; "somebody gives them [to him] silently; they put them into [his] head." Sometimes some words come to him; he does not think them, "the words just show up in [his] system." It seems to him also as if some one else thinks in him, "as if I had two or three people with me." He has also the experience of having an alter ego (*Doppelgänger*). Sometimes even his emotions are experienced as disconnected from his ego: "In my stomach there is something, it feels like anger." "In the teeth it feels like anger, as if they would want to bite, to grab everything." Another time he said: "They put some glorious feeling inside of you, as if you had done something great."

Analogous disturbances are to be observed in regard to the psychomotor activity. His own actions have partially lost their usual relation to the ego. They are excluded from the self and appear to the patient not as his own action but as something done to him. An example of his usual complaint of this sort is: "When I ate this morning I felt as if somebody else's head would also be there and would eat with me. It feels like other people would stick their head into my head. When I am chewing it seems that another tongue comes and takes the food." On another occasion he said: "When I do some work, like swabbing, somebody else is working with me. Just like another person stepped in. . . . It is as if they would be able to put their head in yours, to fit their shoulders, their hands, their legs into yours. When you move they grab; sometimes it seems they are scared that you would fall. They try to help you, but they are clumsy." Once when the patient was turning the pages of a book he remarked: "It is as if a couple more pair of hands would try to do the same thing as I do."

At other times, the portion of muscular activity disconnected and estranged from the ego is not of such cooperative character as indicated in the previous examples. That is, the movements often do not have the same direction as the patient's conscious intention, but they intrude as a disturbing external force into the course of his consciously intended activities. When the patient intends to do one thing, "they try to make me do something different," he feels like a "mechanical man." Once he said: "It is hard to control the tongue, they just drop some words on your tongue. They [conscious intention and "influencing" force] fight like devils. My tongue is heavy, like if somebody would hold it."

Often he refers to rather general inhibition of his muscular activity by a force which seems to him to come from outside. For example: "I feel cased, as if my body would be in a case; I haven't enough place to move. It feels as if invisible things would surround me; a lot of pressure is against my body. It is like cellophane or fluid glass or celluloid paper; one can't see it, but when I move, it hinders, it binds." "My body feels too short for me; my whole body feels like a woolen suit which was in the rain and became wet, then dried out and became short. When you move, it stretches, it binds." "If I try to move I feel like drawn back, grabbed from behind. It feels as if there would be glue on the chair. When I start to stand up, I am pasted." The patient describes well the experience of the inhibition of his muscular activities. These inhibitions are due to contractions of muscles, which, because they have lost their ego-reference, are experienced as an external resistance.

This group of phenomena imply that dissociated tendencies excluded from the conscious self possess a part of the patient's motor function. In this paper the mechanism of this dissociation will not be entered into. Here only the fact is important that the muscular activities and tendencies to muscular activities which have lost their connection with the ego generate in the patient changes in the

muscle tonus which, precisely because they have lost their particular ego-reference, are experienced not as voluntary changes of innervation but as foreign forces. In the first section it was pointed out that the pull exerted by the involuntary contraction of a muscle has the same psychologic effect as any foreign force acting on the body. The dissociated changes of muscle tonus described previously being accounted for as external forces, one may expect that there will appear spontaneously all the phenomena which can be observed when one experimentally induces an involuntary contraction of a muscle in the subject, e. g., by increasing or diminishing the weight of an object supported by the subject without his knowledge (experiments of Ponzo). Therefore, one may expect to find in my patient all the phenomena which can be observed following experimentally induced involuntary contraction of muscles, such as spontaneous sensations of heaviness and lightness, deformation of the postural model of the body and an impression of an emanating light substance.[13]

Sensations of Extreme Lightness and Heaviness of the Body, Deformation of the Postural Model of the Body, the Second Form and the Emanating Substance.—When one lifts or carries an object and the force applied to it is disconnected from the ego and therefore the contraction of the muscles is partly or entirely accounted for as a foreign force, the object (according to the theory expressed in the first section) must appear lighter. This change of weight extends also to the perception of the weight of one's body. In fact, my patient often complains about the extreme lightness of his body. He once said: "When I move my arms they are so light that I can hardly realize they are there. . . . Sometimes I have a nice heavy backbone, a well filled body, but other times it feels like air." Another time he said: "No weight to my head; I haven't now any skull, it is too light, it is of wood." The sensation of lightness often extends to the whole body. He often complains: "When I am walking I don't seem to walk on the ground but on air; my body is too light, I don't feel any weight, I am like a shadow."

It is significant that this sensation of lightness occurs when the patient executes a voluntary movement (moving the hands or walking) and is not likely to occur when he is sitting quietly. The sensations of lightness of the body are usually accompanied by the impression of motor influences ("somebody is doing with me," etc.). This is in agreement with my interpretation, since it shows that the sensation of lightness arises on such occasions when a nonego-referred contraction of muscles is also present.

The sensation of lightness of the body is also responsible for the sensation of flying. The patient sometimes complains: "In walking I feel a sudden twist as if I would go right up in the air, like a balloon." He also often says that he feels "shooting up into space."

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13. Pathologic changes or experimental irritation of the vestibular apparatus cause phenomena which are similar to these somatic sensations. This has been demonstrated in the experiments with elevators by Parker and Schilder (Parker, S., and Schilder, P.: Das Körperschema im Lift, Ztschr. f. d. ges. Neurol. u. Psychiat. **128**:777, 1930). This is, however, no argument against the muscular origin of these phenomena. The vestibular irritation does not directly cause the phenomena, but it produces changes in the muscle tonus, and these changes are responsible for the somatic sensations. The phenomena can be elicited by any involuntary change of muscle tonus, and the vestibular tonus is only one of the muscular phenomena which are able to produce the described sensations.

Less frequently the patient complains about unusual heaviness of parts of his body. Spontaneous impressions of heaviness may arise (according to the theory presented in the first section) when there is an involuntary, unintentional contraction of the muscles acting in the direction opposite to that of voluntary contraction. This occurs, for example, when the patient has the impression that his tongue is very heavy, when there is a "foreign force" which tries to make him tell something different from what he wants to say. The interfering contraction of the muscles is, however, in the majority of instances perceived not as weight but as an external resistance. "The muscles feel tight." "There is a grip on them." "There is some pressure against the body." "There is no space to move."

Sometimes the patient complains that when he carries some weight he receives what he calls a "paralyzing shock." This "shock" comes suddenly and knocks down his arm. When he is carrying a weight on the shoulders this impression extends to the whole body. He says that it is as if he would be hit on the back and pushed down, and he compares this sensation with the impression one has in an automobile when it comes to a sudden stop. These phenomena are related probably to a sudden relaxation of the muscles, as it can be observed at the beginning of sleep.[14] According to the theory expressed in the first section, the decrease of muscle tonus must intensify the sensation of heaviness.

The unusual impressions of heaviness and lightness are not continuous. They are directly dependent on the disconnection of muscular activities from the ego. The phenomena of the disruption of ego-reference in persons with schizophrenia are not continuous; they do not extend to all experiences of the patient but affect only single experiences. Kronfeld[15] first called attention to these facts. He tried to discriminate between the schizophrenic disturbances of self-awareness and and disturbances of self-awareness in states of depersonalization. The latter disturbances are, according to Kronfeld, qualitative modifications and more diffuse, while in the typical schizophrenic disturbance there is a "loss of the consciousness of the active ego," and this loss is not general but affects well circumscribed single actions. On this basis one can easily understand why the phenomena dealt with in this section are not continuous but occur sporadically. I suspect, however, that also the more diffuse disturbances of self-awareness which one observes in states of depersonalization may occasionally cause experiences in the field of muscle sensations similar to those described here. In fact, in histories of cases of depersonalization[16] one often finds complaints about the extreme lightness of the body.

Changes of muscle tension, when they are excluded from the self-awareness, act in the same way as do external forces, and thus they may produce not only spontaneous sensations of heaviness and lightness but also deformations of the postural model of the body similar to those observed in Ponzo's experiments, in which the weight of an object supported by the subject was diminished or increased without the knowledge of the subject. In the experimental situation,

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14. In a recent article Kloos (Kloos, F.: Gedankenabreissen mit Tonusverlust odor Schwindelanfällen bei Schizophrenie, Psychiat.-neurol. Wchnschr. **36**:541, 1934) reported marked, sudden drops of muscle tonus in patients with schizophrenia. Kloos' article is only a short résumé, and a more detailed report is announced; for this reason I cannot enter here into further discussion.

15. Kronfeld, A.: Ueber schizophrene Veränderungen des Bewusstseins der Aktivität, Ztschr. f. d. ges. Neurol. u. Psychiat. **74**:15, 1922.

16. Schilder, P.: Selbstbewusstsein und Persönlichkeitsbewusstsein, Berlin, Julius Springer, 1914.

by the diminution of weight the supporting limb seemed to raise, or elongate, itself; the increase of weight had an opposite effect but of less degree than the decrease of weight. Analogous to these phenomena are some of the comments of patients: "Today when I carried the laundry [on the shoulders] I seemed to become shorter, my back seemed to give way; when I put down the laundry I became higher, I gained." This description resembles closely the experimental situation in which the weighted object is placed on the subject's head and the weight is then lightened. The patient also complains that when he is walking he feels "suddenly lifted up, the whole body becomes light, it is like growing into air." "When walking on stairs I feel sometimes like a lift-up, like by air pressure; my spinal column expands like rubber; then it snaps together again." "When I stand up from the chair it feels as if a spring underneath the spinal column would give me a push. It is like when your foot sticks in the mud; when you pull it out, it feels like a spring." He has experienced shortening of his body: "When I carry a weight, my spinal column shrinks. . . . In the morning when I stand up, my spinal column snaps. . . . Sometimes when I am walking they suddenly pull down my whole body, like the shade of a window." The impression of elongation and shortening of the body must be very intensive. He reported once: "This morning after I put away the rugs and jumped down from the table, it felt like jumping down from a high building; my knees came up nearly to my stomach. I felt like somebody would force me down." I asked him to step up on the chair and then step down and asked what he felt. When stepping up he felt an elongation of the body "as if the middle of the body would be an elastic"; when stepping down he said: "You are pushed down, as if your feet would go to meet your head, like an accordion."

The conditions responsible for the spontaneous sensation of lightness and elongation of the body or of parts of the body may give rise also to the impression of a light substance passing through the muscles and emanating from the body; it is as though another limb, or another body, made of a very light substance, were leaving the body. This experience in my patient is common. "When I move I seem to lose, it seems that the whole body leaves me. The spinal column or something passes invisibly through the flesh. As if somebody would be able to get hold on me, like an eagle, and draw my flesh and bones away." "They pull out another person from my body. I feel that my form leaves me; not exactly my form but a second form." "It is like some strong man would be able to yank out another form from mine. When they take that out of me, it feels like a quick sensation, like a jar." The patient relates that sometimes it seems to him "as if another person would step out" of him. Once during the interview, he remarked spontaneously: "Now, when I leaned back on the chair my body seemed to slide out of me. Not exactly my body, but another form like mine." This kind of experience may be responsible, at least in part, for his idea that there is another person like him, an alter ego (*Doppelgänger*).

These phenomena are often experienced not as a "second form" leaving the body but as a rather indefinite light substance emanating from the body. "These invisible things bother me. It is hard to explain; parts are flying out of me. When I move quick, something is flying up from me, like air, like wings."

It is interesting that with the impression of an airy substance flying out of him, often a feeling is associated that this substance will hit people. "The worst thing is that when this invisible thing swings away from me, it feels that it hits somebody. You know, if somebody does something against me, I try to forget, let it go, but this thing hits out from my body automatically, shoots through space and hits people." One sees here that the patient brings this last phenomenon in connection with his repressed hostility, and probably he is right. He made it a

principle of life to be friendly to people under any circumstances and never to show or admit hostile feelings. But behind this friendly appearance a wealth of hostile feelings is clearly evident. It is known that changes in muscle tension are always present in a person in an affective state. It would be impossible to experience genuine rage with relaxed muscles. It was mentioned before that my patient experiences his affective states as something which does not belong to his self. "In my system there is something, it feels like anger." "In the teeth it feels like anger, as if they would want to bite." Together with the feeling of anger, the tonus generated by it is disconnected from the self and may cause the same changes as any other unintended change in tonus or an external force.

It is interesting to note in this connection that Schilder [17] conceived of the unity and the disintegration of the postural model of the body in connection with narcissism and sadism, respectively. It is not clear to me by what "mechanism" sadism and narcissism could influence the perceptual experience of the body. According to what I stated before, repressed affects may generate contractions of muscles, which, again may cause a deformation of the postural model of the body. This might well be the mechanism of the connection postulated by Schilder, though perhaps Schilder would assume a more general and more fundamental relation between the postural model of the body on the one hand and sadism and narcissism on the other.

III. DISTURBANCES OF THE POSTURAL MODEL OF THE BODY

Modifications of the Postural Model of the Body.—In this section a group of somatic complaints will be discussed which represent modifications of the postural model of the body.

The concept of "schema," or "body diagram" or "postural model of the body," was first introduced by Head [18] (under the name schema). Pick and others made valuable contributions to the problem, but Schilder recognized the full importance of the problem both from a neurologic and from a psychiatric point of view.

Head used to demonstrate the existence of a schema by pointing to the fact that one can become aware of the position of any part of the body at a given moment, even if the postural recognition is not constantly in the focus of consciousness. According to Head, one is in possession of a schema of one's posture at any moment. "Every new posture or movement is registered on this plastic schema and the activity of the cortex brings into relation with it each fresh group of afferent impulses evoked by a change in the position of the body." The schema is, according to Head, not a conscious image, and the registration of postural changes on the schema takes place on physiologic levels. This schema is the "standard against which all postural changes are

17. Schilder, P.: Vestibulo-Optik und Körperschema in der Alkoholhalluzinose, Ztschr. f. d. ges. Neurol. u. Psychiat. **128**:784, 1930.

18. Head, H.: Studies in Neurology, New York, Oxford University Press, 1920; Aphasia and Kindred Disorders of Speech, New York, The Macmillan Company, 1926.

measured. Every recognizable change of posture enters into consciousness already as a measured postural change." [19]

Schilder [20] used the concept of "body diagram" (*Körperschema*) to indicate the conscious representation of one's own body. He defined the body diagram as "the spatial representation that one has of oneself." The postural model of the body is not built up of single sensations. The localization of somatic sensations "takes place only in reference to this postural scheme." [21] The existence of the postural model of the body shows itself impressively in persons who have lost a leg or an arm but continue to have perception of the old limb. This is the phenomenon of fantom limb, which, according to Weir Mitchell, who first described it, is absent in only 3 per cent of cases after amputation.

When the body is brought into an unusual posture, the postural model of the body does not shape itself perfectly according to this unusual change, and many illusions of the type of the aristotelian illusion and its variants (Ponzo [22] and von Skramlik [23]), the Japanese illusion [21] and similar phenomena arise.

The postural model of the body is the whole, or *Gestalt,* into which the sensory data coming from the various parts of the body are fitted and form the experience of the body-self. The latter is again a part of a larger unity, that of the conscious self.

Some of the phenomena discussed in previous paragraphs, such as the impression of elongation or shortening of the body, or a part of it, are changes of the postural model of the body. In this section some other deformations of the postural model of the body present in my patient and in a certain number of other schizophrenic patients whom I have studied will be discussed. The enumeration will not be complete; only the most common complaints will be reported.

1. There is a definite impairment of the unity of the body. The patient often complains that "the body doesn't seem to stay together"; he feels "loose-jointed" or "falling apart." My patient says that "the head and the neck do not connect." Another patient says that "there is no connection between the upper and the lower

19. It does not seem to me that this integration takes place entirely without the participation of consciousness. It is true that the awareness of one's posture is not demonstrable at every given moment, but, on the other hand, the integration of new changes into the schema requires that the subject be in a conscious state when the change occurs.

20. Schilder, P.: Das Körperschema, Berlin, Julius Springer, 1923.

21. Klein, E., and Schilder, P.: The Japanese Illusion and the Postural Model of the Body, J. Nerv. & Ment. Dis. **70**:241, 1933.

22. Ponzo, M.: Intorno ad alcune illusioni nel campo delle sensazioni tattili, sull' illusione di Aristotele e fenomeni analoghi, Arch. f. d. ges. Psychol. **16**:307, 1910.

23. von Skramlik, E.: Varianten zur Aristotelischen Täuschung, Arch. f. d. ges. Physiol. **201**:302, 1923.

part of the body." It seems unlikely that this type of disturbance would be related to a particular condition in the peripheral sensory organs, and it seems rather to be due to a central modification of the experience of the body-self. Similar phenomena may occur in normal persons in the hypnagogic state, which is characterized by marked disturbances of self-awareness. Once I had occasion to observe the disintegration of the body-self in one of my normal subjects, who was terrified because just after awakening from a superficial sleep he felt his arm resting on the body of a huge serpent lying in his bed; it took a few seconds before he realized that his hand was resting on his own thigh.[24] This happened just after awakening when the postural model of the body had not had time to reintegrate itself.

2. The continuity of the body-self is definitely impaired. One experiences one's body usually as continuous in space, though there is by no means a continuous sensory stimulation all over the body. This is similar to the blindspot in the retina, which is not sensitive and yet does not cause a perceptible hiatus in the visual field. The same is true with the sense of taste. The sensation of taste is spread over the surface of the tongue, though only a relatively small part of it is provided with the specific organs of taste.[25] There are similar conditions in the field of cutaneous sensibility: A ring pressed on the skin may be perceived as a circular surface.[26] The filling out of the "blindspot" of the body is probably a function of the postural model of the body. It thus comes about that one usually perceives the body not as number of discontinuous focal sensations but as a continuous and more or less homogeneous mass. But the continuity and homogeneity of the body are very labile. If one directs attention to the perception of the body and wishes to bring it to the focus of consciousness, one notes definite sensations at a given moment only in certain parts, while the inpression of a great part of the body remains hazy or is not perceived at all (Klein and Schilder,[22] von Skramlik [27]).

In some schizophrenic patients (and in patients with other conditions, in which there is a disturbance of the postural model of the body) the perception of discontinuity of the body takes a characteristic form. These patients complain about emptiness of the inside of the body and of the skull. My patient complains that he has "no inside of the body, but only a frame." He says that when he eats "the food is falling in a vacuum." "Behind the chest is nothing, only a big hole." "The inside of the skull doesn't feel at all, it is like air." "The stomach and the top of the skull are open." It is interesting to observe that patients having these disturbances complain about them in the same words, which shows that these are not random bizarre ideas but must have a common basis.

There is a definite perceptual basis for the localization of these huge "blindspots" in the body. Hartmann and Schilder [28] proved that the inside of the body is perceived as weight. The heaviness is perceived in the lower parts of the body; when the subject is in an upright position, it is felt at the base of the skull,

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24. Angyal, A.: Der Schlummerzustand, Ztschr. f. Psychol. **103**:65, 1927.

25. Ponzo, M.: Analogie fra le illusioni determinate del punto ceico retinico e quelle dipendenti dalla zona linguale ageusica, Riv. di antropol. **20**:3, 1916.

26. Cinaglia, L.: Riempimento soggettivo di spazi vuoti nel campo delle sensazioni cutanee, Riv. di psicol. **8**:1, 1912.

27. von Skramlik, E.: Ueber Tastwahrnehmungen, Ztschr. f. Sinnesphysiol. **56**:256, 1925.

28. Hartmann, H., and Schilder, P.: Körperinneres und Körperschema, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:666, 1927.

at the lowest part of the abdomen and in the legs, while the inside of the upper part of the head and of the body feels rather empty. This uneven distribution of the sensations in the body, present even in normal persons, is extraordinarily emphasized in the group of patients to which I am referring.

The spontaneous sensation of lightness must have an important part in producing the feeling of emptiness. Only when there is a sensation of lightness does the patient feel his body and skull "empty" and "open." Also, in Parker and Schilder's [13] experiments with elevators when the light substance seems to pass out of the body and the body feels as if it were becoming light there is an impression as if the inside of the body were emptied.

The impression of emptiness of the body gives rise to a group of peculiar complaints which I often observe in this type of patient. The patient says that the food he eats "immediately disappears." "It evaporates just like steam." "It is taken out." "Somebody draws it away, removes it in some invisible way." "It seems to me as if it would be only a make-believe eating; it is like when somebody is drunk and believes he sees a green elephant which is not there; just the same with my food." "The food does not reach the stomach at all but when it passes the throat it disappears." "My opinion is that it would be better not to eat. It is no fun to see that my food disappears while the others can hold their food." One observes occasionally that patients in such a state refuse to eat, but it is more usual for them to have a ravenous appetite. They overeat because they try again and again to "fill up the stomach." [29]

The impression of the disppearance of food may be another expression of the sensation of emptiness.[30] One must, however, assume that behind these complaints there lies more than the sensation of emptiness. The extreme concern about eating, the feeling of guilt connected with eating and similar complaints suggest strongly that something essential, closely connected with some central factor of the psychosis, is expressed in such complaints. But in this paper only the perceptual elements of the symptomatology are discussed.

3. Another deformation of the postural model of the body consists in an impression of a reduction of the dimensions of the body, whereby sometimes the third dimension of the body seems to be nearly eliminated. The patient says that he feels extremely thin, that his "clothes only hang [on him] like on a skeleton." "The space between the chest and the back is so short that you don't feel altogether human, but like an accordion." "Nothing is behind my chest. I have no back. My chest touches the back of the chair." "The front of the stomach and the back meet." "The chest and the back touch each other." "I feel flat like those signs on the side of the road." It is difficult to say what is the basis for these particular complaints, but they must have something to do with

29. Of course, I should not generalize and conclude that the negativistic attitude toward eating and overeating in schizophrenic patients is always due to a sensation of emptiness of the body. Recently, Miller made a careful investigation of the attitudes of certain schizophrenic patients toward the ingestion of food and liquids (Miller, W. R.: Psychogenic Factors in the Polyuria of Schizophrenics, J. Nerv. & Ment. Dis., to be published).

30. This might go back to the theory of the child about the inside of the body. Schilder and Wechsler (Schilder, P., and Wechsler, D.: Was weiss das Kind vom Körperinneren? Internat. Ztschr. f. Psychoanal. **20**:93, 1934) found by questioning children about the inside of the body that younger children often believe that their bodies are filled with food.

motor activities which become disconnected from the ego, because the complaints about flatness of the body are always accompanied with complaints of motor influences and sometimes with complaints about a light substance passing out of the body.

4. The differentiation between directions in the body, like right and left, below and above, behind and in front, is also part of the postural model of the body. The distinction between these directions may be impaired in persons with certain types of lesions of the brain. The patient whose case is used in this paper for demonstration has no disturbances of this kind other than some uncertainty in the distinction between left and right. There are also some vague complaints that his "left and right side are muddled up . . . . The muscles of the left side are on the right side," and vice versa. As a child he was left-handed. A test for handedness revealed left-handedness. He was forced in school to use the right hand. This might have something to do with his uncertainty about right and left.

5. A peculiar disturbance of the postural model of the body consists in the impression of displacement of single parts of the body. Patients with such a disturbance complain that "the arms are creeping into the chest"; "the head sinking into the body," etc. It seems probable that such phenomena are based on changes in muscle tonus and on muscular sensation due to changes in tonus.

6. The perception of space, its organization, has certainly to do with the postural model of the body. The problem of such a relation is not yet settled, but there are a number of facts which show the existence of an intimate relation. In persons with certain types of lesions of the brain, disturbances of the postural model of the body and disturbances of perception of space (and disturbances of praxia) go side by side. My investigations on orientation in space,[31] suggest that the postural model of the body and the orientation in the outside space (especially in *Naheraum*) are based on the function of identical physiologic and psychologic mechanisms. On the basis of my observations I inferred that there must be a not clearly conscious, automatic registration of every change of the relation between one's body and the environment. This registration is probably the function of the same mechanism which registers every change in the position of any part of the body, of which Head spoke. I have shown that it is nearly impossible to influence arbitrarily by imagination the orientation schema representing the relation of one's body to the nearest environment, and only actual changes of relation of position between the body and the environment are registered by the mechanism which I postulated. The same thing is true with regard to the postural model of the body. Schilder, Riese, Adler and Hoff,[32] Ehrenwald[33] and others have clearly demonstrated that the fantom limb has the same position as the limb had in the moment when it was lost. This shows that in the postural model of the body only actual changes of position are registered. After the limb is lost, such change is no longer possible, and therefore on the postural model of the body the last position which the limb had remains fixed.

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31. Angyal, A.: Die Lagebeharrung der optisch vorgestellten räumlichen Umgebung, Neue psychol. Stud. **6**:293, 1931; Ueber die Raumlage vorgestellter Örter, Arch. f. d. ges. Psychol. **78**:47, 1930.

32. Adler, A., and Hoff, H.: Beitrag zur Lehre vom Phantomglied, Monatschr. f. Psychiat. u. Neurol. **76**:84, 1930.

33. Ehrenwald, H.: Verändertes Erleben des Körperbildes mit konsekutiver Wahnbildung bei linkseitiger Hemiplegie, Monatschr. f. Psychiat. u. Neurol. **75**: 89, 1930.

The disturbances of the experience of space in my patient are similar to the disturbances he experiences in his own body. In the same way as he experiences a shrinkage of his body, he has also the impression that the whole space is restricting itself. He has this experience especially while riding in street-cars. "Sometimes in the street-car it seems to me as if the people would sit on top of me, they are so near. I mean they sit in their places, but the car becomes small, is folded up like an accordion." This impression is accompanied by a sensation of pressure against the body and with an impression of motor influences.

Another peculiar complaint is the following: "When I go along the corridor it feels as if a flexible glass would be put through my body and touch the wall. When I go it feels as if I would push everything before me like a snow-plow; as if the glass would hold me back." This complaint is evidently based on motor functions which become disconnected from the ego and which can be explained in the following ways (*a*) He feels himself held back by involuntary changes in tonus in his body; (*b*) he projects the hindrance of his movements into the environment (the walls hold him back), but (*c*) he sees that there is no visible connection between him and the objects of the environment—hence, the idea that he is connected with the walls by "flexible glass." The following complaint expresses essentially the same thing: "When I go on the street or through a door, it feels as if I would not have enough place, as if I would touch the walls. I feel large—I mean, the body is the same size, but the air around is large. If I go by a tree, I touch the tree with my air and its holds me back."

7. One usually regards the complaint that parts of the body are not alive as a disturbance of the postural model of the body. Such complaints by my patients are: "Parts of the body are of wood." "The skin is papery." "Underneath the skin there is no flesh, but hairs grown inside, or a layer of silk." "The ribs are only set in." "I have no throat, but only a brace."

As will be seen, many of the phenomena discussed in this section are definitely related to the presence of contractions of muscles which have lost their specific relations to the ego and to those secondary perceptual experiences which are based on nonego-referred contractions of the muscles. However, not all the phenomena described in this section seem to be completely explained on this basis. Such disturbances as the lack of unity of the postural model of the body or the impression of displacement of parts of the body should probably be explained on some other ground. Psychologically they can be understood as a part of the general disturbance of self-awareness. The problem, however, has also a neurologic aspect, which will be discussed in the next section.

The Interparietal Syndrome.—Disturbances of the postural model of the body have been described in persons with certain types of cerebral lesion. The disturbance manifests itself in various symptoms: disorientation on one's body (autotopagnosia), disturbances of the unity of the body, displacement of parts, an impression that parts of the body are lifeless or do not belong to the person, etc.

Head [18] reported a case which suggests the cortical localization of the postural model of the body. Head's patient, after an amputation of a leg, experienced having a fantom foot and leg. Later, after the

occurrence of a cortical lesion, the impression of the fantom leg immediately disappeared. "The stroke which abolished all recognition of posture destroyed at the same time the phantom limb."

The anosognosia of Babinski, called also Anton's symptom, belongs to the same order of phenomena. Such patients having, for example, hemiplegia, are not aware of their disabilities.

Recent efforts to localize the postural model of the body have pointed definitely to certain regions of the parietal lobe and to the borderline zones of the parietal and occipital lobes. The cortical tissue along the interparietal sulcus, the gyrus angularis and the posterior part of the gyrus supramarginalis seem to be the most important parts for the postural recognition and related functions. On the basis of available material, Hoff [34] undertook to determine a more specified localization within the aforementioned cortical regions. As the experiments of Hoff and Pötzl [35] showed, the optic thalamus also has importance with reference to the postural model of the body.

Gerstmann [36] described a syndrome consisting of a disturbance in differentiation between the fingers of the hand, disturbance of the discrimination between the right and the left sides, agraphia and acalculia. Lange [37] tried to reduce the syndrome of Gerstmann to a single basic disturbance, namely, to "the loss of the category: direction in space." Pötzl and Hermann [38] succeeded in localizing the syndrome of Gerstmann in the transitional zone of the inferior parietal and middle occipital gyrus.

Besides the observations at autopsy, most significant are the experimental studies for the anatomic localization of the postural model of the body. Hoff and Pötzl [35] reported experiments on three subjects with bony defects in the parietal region. They injected intravenously 10 cc. of a product containing cinchophen sodium, sodium salicylate and p-aminobenzol-di-ethylamino-ethanol hydrochloride, which, as Hoff had noted previously, has an elective depressor action on the optic thalamus. The area of the bony defect was frozen with ethyl chloride

34. Hoff, H.: Die zentrale Abstimmung der Sehsphäre, Berlin, S. Karger, 1930.

35. Hoff, H., and Pötzl, O.: Experimentelle Nachbildung von Anosognosie, Ztschr. f. d. ges. Neurol. u. Psychiat. **137**:722, 1931.

36. Gerstmann, Y.: (*a*) Fingeragnosie: Eine umschriebene Störung der Orientierung am eigenen Körper, Wien. klin. Wchnschr. **37**:1010, 1924; (*b*) Fingeragnosie und isolierte Agraphie, ein neues Syndrom, Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:152, 1927; (*c*) Zur Symptomatologie der Hirnlesionen im Uebergangsgebiet der unteren Parietal- und mittleren Occipitalwindung (Das Syndrom: Fingeragnosie, Rechts-Links-Störung, Agraphie, Akalkulie), Nervenarzt **3**:691, 1931.

37. Lange, F.: Fingeragnosie und Agraphie, Monatschr. f. Psychiat u. Neurol. **76**:129, 1930.

38. Pötzl and Hermann, quoted by Gerstmann.[36c]

in order to inhibit the function of the corresponding cortical region. Under such conditions, marked disturbance of the postural model of the body and phenomena similar to depersonalization were observed.

Anatomic studies on the localization of the postural model of the body were summarized well by Schilder,[39] who concluded that fields 39, 40 and 19 of Brodmann and the sensory visual band of Elliot Smith "are indispensable for the inner experience of the body."

The "interparietal syndrome" has been studied mostly in persons with neuropathologic disturbances. Recently Gurewitsch [40] observed this syndrome also in persons with various kinds of psychoses. Gurewitsch divided the symptoms which make up the interparietal syndrome into two groups: the disturbances of the postural model of the body and several sensory (principally visual) phenomena. Gurewitsch distinguished two types of interparietal syndrome: (1) the posterior (parieto-occipital) type, in which visual symptoms and general disturbances of the postural model of the body prevail, and (2) the anterior (parietopostcentral) type, with partial alterations of the postural model of the body. In two papers Gurewitsch reported fifteen cases, among which were cases of cerebral syphilis, epilepsy, hysteria, epidemic encephalitis, angioneurosis, head traumatism and schizophrenia (four cases of the last).

The similarity of the disturbances of the postural model of the body in patients with lesions of the parietal lobe to the symptoms noted in certain schizophrenic patients is suggestive. One could also point to histopathologic data in favor of this relation. Atrophy of the parietal lobe is not an unusual observation at autopsy on patients with schizophrenia. Von Angyal,[41] who recently reported a few cases of schizophrenia with the the interparietal syndrome, stated that "on the basis of the most recent histologic investigations (Miskolczy, Hecht) it appears as doubtless that the lobulus parietalis inferior, including the gyrus supramarginalis, the gyrus angularis and the area parietalis basalis belong to those cortical regions which are most seriously damaged by the schizophrenic process." Moore, Nathan, Elliott and Laubach [42] concluded, on the basis of encephalographic studies of sixty cases of schizophrenia, "that there are atrophic cortical changes involving the

39. Schilder, P.: Localization of the Body Image: Postural Model of the Body, A. Research Nerv. & Ment. Dis., Proc. **13**:466, 1934.

40. Gurewitsch, M.: Ueber das interparietale Syndrom bei Geisteskrankheiten, Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:593, 1932; Weitere Beiträge zur Lehre vom interparietalen Syndrom bei Geisteskrankheiten, ibid. **146**:126, 1933.

41. von Angyal, L.: Zur Bedeutung des interparietalen Syndrom bei der Schizophrenie, Arch. f. Psychiat. **102**:107, 1934.

42. Moore, M. T.; Nathan, D.; Elliott, A. R., and Laubach, C.: Encephalographic Studies in Schizophrenia (Dementia Praecox), Am. J. Psychiat. **12**:801, 1933.

fronto-parietal-occipital areas to a greater or lesser degree. The atrophy is most marked, as is manifested by the size of the air markings, over the parietal area."

In order to determine whether one is justified in assuming that there is some neuropathologic involvement in the case which is reported here, various examinations were made.

The patient's past history shows that birth was difficult. When he was 17 he suffered an injury to the head in a street-car accident (bumped his forehead on the back of the seat). He did not lose consciousness completely and remained in the hospital for only a few hours. After this accident he complained for a time that his "eyes were bothering him."

Neurologic examination revealed few positive signs. There is a slight facial paresis on the left side, which seems to involve all three branches of the facial nerve. The transverse frontal folds decline toward the left, the left side of the face is flatter than the right, and the left angle of the mouth droops slightly; the patient cannot close the left eye when the right eye is open, and he cannot blow out the right cheek. Relatives report that a slight asymmetry of the face has been present ever since they remember. There is the suggestion of a slight increase in the tendon reflexes on the left (biceps, patellar and achilles tendons). There is a suggestion of Hoffmann and Rossolimo reflexes on the left. There is past-pointing with both hands, which is slight (from 1 to 4 cm.) but consistent in direction, to the left. On one occasion, which was marked by an exacerbation of his psychotic symptoms in general, the past pointing was from 15 to 18 cm. At the same time, the patient had the impression that the whole space was moving and was convinced that if the examiner put his foot close to his (the patient's) foot the examiner also would feel this movement. There is a general clumsiness in his movements. Occasionally, one can observe small sudden jerks or muscular twitching. Muscular strength measured with the dynamometer was: right, 110, and left, 95.

A series of examinations was made in order to test the functions which depend on the postural model of the body. The examinations of cutaneous (touch) localization gave the following results:

1. There was a tendency to irradiation of tactile sensation. When a single point was stimulated, the patient often perceived it as a circular surface. Lines drawn on the skin he usually perceived as a band about ½ inch (1.2 cm.) broad. Similar phenomena were observed by Stengel in a case of thalamic lesion.[43]

2. There was a tendency to polyesthesia. When a single point was touched, he sometimes perceived it as two or three points near each other. At other times he had the impression that a larger number of points, "about five or six," were touched.

3. A phenomenon resembling dyschiria was also observed several times. When a point on one side of the face was stimulated he perceived it normally, but he sometimes perceived a second faint sensation, "like a rebound," on the opposite side of the face. But while with genuine synchiria the second sensation is localized symmetrically or almost symmetrically to the first, in my patient there was little tendency to symmetrical localization.

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43. Stengel, quoted by Stein, H., and von Weigsäcker, V.: Zur Pathologie der Sensibilität, Ergebn. d. Physiol. **27**:657, 1928.

4. On certain regions of the body the errors of localization showed a constant direction: On the forearm (between the elbow joint and the wrist) the sensation was constantly localized more distally, and on the chest more medially, than the point actually stimulated. The error was usually about 4 cm. but often was even 10 cm. This type of error of localization has probably no pathologic significance. Similar errors were described by Ponzo in normal persons.[44] It is true that the amount of error he reported was considerably smaller than that in my patient, but this might be due to the difference in technic. In experiments with normal subjects there is the task of localizing the sensation within a previously fixed small cutaneous area, while in my experiments no such restriction was made.

As was previously mentioned, lesions of the gyrus angularis may impair the ability to discriminate between right and left. My patient has some vague complaints of this sort, saying that "the muscles of the left and right hand are muddled up" or that he feels that he could write better with his right hand if the fingers were arranged in the opposite direction, i. e., if the thumb were at the place of the little finger, etc. If the patient is asked to show his right or left hand he often makes an error but then he corrects himself.

To determine the ability to discriminate between right and left, the following test was given: The patient was asked to indicate on a circle, with twelve markings of equal distance, where the arms of the clock would stand at a given time. The first few reactions were wrong: twenty minutes past nine he indicated by putting the long arm at 9 and the short arm at 4. When the correctness of this solution was questioned, the patient first insisted that the long arm is for the hours and the short one for minutes. Instead of ten minutes to six, he showed ten minutes past six, but he read it correctly as ten minutes past six. After a few trials he made no more errors, but he needed a rather long time for the solution of the task.

If two or three fingers of one hand are shown to the patient, he can imitate it correctly, but if both hands (from three to five fingers) are involved in the test, he makes numerous errors.

The patient makes many errors, especially on certain days, in simple calculation and writing after dictation, but the type of error does not suggest the presence of agraphia or acalculia.[45] In reading, the patient makes numerous errors, one or two in a line. The most common error seems to be due to the fact that he grasps only the general picture of the word and not its elements. He has read the word receptive, receptacle; motives, notes; intention, invention; appearance, appeal; anticipation, anticoation; earliest, exist; recording, reckoning; strata, stature; merely, lovely; etc. Somewhat uncommon words are always misread, because if he does not recognize the word as a whole he seems to be unable to build it up from its components. For example, when in a test the word "psychological" occurred (the patient knows and uses the term "psychological laboratorium"), he was blocked and took about five minutes and then read "paisographical."

The previously mentioned areas of the parietal lobe seem to exercise a controlling and inhibiting action on reflex changes of muscle tonus and lesions of those areas reduce this inhibition. This could be the

44. Ponzo, M.: Osservazioni intorno alla direzione degli errori di localizzazione negli spazi intercostali, Atti. d. r. Accad. d. sc. di Torino **46**:3, 1911; Sulla localizzazione delle sensazioni tattili e dolorifiche, Arch. ital. d. psicol. **1**:88, 1925.

45. Most of the tests for writing and calculation were given by Dr. J. McV. Hunt in connection with another study.

ground of the patient's complaint that the automobiles on the street "exert a suction on [his] body." Also, normal persons when close to a rapidly moving object have an involuntary tendency to move in the same direction. This tendency is much stronger in my patient, possibly because of lack of cortical inhibition.

On the basis of the results of the neurologic examination and of the objective tests, one can state only that there is a suggestion of some neurologic involvement, possibly in the parietal lobe; the objective findings are not sufficiently clearcut to allow any further conclusion. It might be added that in other patients with similar symptomatology who have come under my observation the objective findings were even more scanty than in the patient whose case is reported here.

Gurewitsch postulated the presence of the interparietal syndrome in certain schizophrenic patients on the basis that the subjective complaints of these patients are strikingly similar to the phenomena observed in persons with a lesion of the interparietal zone. But it is questionable whether this is a sufficient basis for stating the identity of the two phenomena. If such a lesion were present in certain schizophrenic patients, it is reasonable to assume that this would manifest itself in the objective examination of the functions which presuppose the integrity of the postural model of the body. This is, however, yet to be proved. It is of interest to note that in Gurewitsch's report of four cases of schizophrenia there was no mention of the neurologic observations or it was explicitly stated that neurologic examination did not yield positive results. The great similarity between the subjective complaints of some schizophrenic patients and the symptomatology of lesions of the interparietal zone, however, justifies further research in this direction. Considerable clarity might result from a set of objective examinations testing the functions of the interparietal lobe. These tests should be standardized on normal persons. Also, the encephalographic examination of schizophrenic patients who show the previously described symptomatology might give valuable information.

COMMENT

In this paper only a single group of somatic complaints has been analyzed, and it has been pointed out that they have a definite perceptual basis consisting of particular muscle sensations. It would not, however, be admissible to generalize that all somatic complaints of schizophrenic patients have the same basis. It is possible that such vague hypochondriac complaints as "the inside of the body is rotten" and "the intestines are useless" are based on other kinds of sensation or that they have no perceptual basis whatever.

The unusual sensations in the body are not always reported as such, but they are often further elaborated and interpreted by the patient according to his delusional system. For example, if the patient shows a paranoid trend, not only will he complain that his stomach is "open" or that some light stuff is leaving the body, but he will say that "they" open him and "they" take the stuff out of him.

The unusual muscular sensations were explained by the presence of muscle contractions (and relaxations) which have lost their usual relation to the ego and are experienced as external forces. The disconnection of muscular activity from the ego is a manifestation of a general disturbance of self-awareness, which is called a loss of ego-reference. This phenomenon was not further analyzed in this paper but taken as a descriptive fact. The loss of ego-reference seems, from the psychologic point of view, to be a special kind of defense mechanism. While in a patient with hysteria such factors as are not compatible with the rest of the personality are excluded from consciousness (anesthesia, amnesia, etc.), in the group of schizophrenic patients with the previously described symptomatology the disturbing factor is allowed to enter the consciousness, but its "belongingness" to the ego is not recognized and is ascribed to influences from the outside.

In this paper, for the sake of brevity, only one case has been described. Among one hundred schizophrenic patients, only four showed in pronounced form the symptomatology described. The condition in these patients is extreme. If one includes in the group patients who show some of the symptoms described or in whom these symptoms are only transitory, the percentage would be at least 15.

One notes this symptomatology most in patients in the hebephrenic and mixed hebephrenic-catatonic group, though it can be observed also in patients with a definite paranoid tendency. Patients with clearcut paranoia and simple schizophrenia showing this symptomatology have not come under my observation.

SUMMARY

A group of somatic "delusions" manifested by certain schizophrenic patients was analyzed in order to determine whether the delusions are based on sensory experiences. It was decided that these somatic complaints have a definite perceptual basis consisting of certain muscle sensations.

As the basis for further explanation, the following theory of weight perception was presented: (*a*) The intensity of weight perception is directly proportional to the amount of the stretch produced in the muscle by resistance. The stretch must be measured in units of length. An object, therefore, is perceived as being lighter if one increases the

strength of contraction applied in lifting the object, because the same resistance produces less stretch in a strongly contracted muscle than in a slightly contracted muscle. All the factors which influence the amount of stretch, such as the size of the muscle and its physiologic condition, must influence the intensity of weight perception. (*b*) The stretch of the muscle is usually produced by an external resistance, but if an involuntary contraction is present when one lifts an object the involuntary contraction also acts as an external resistance. The presence of involuntary contraction in the agonistic group of muscles while an object is being lifted makes the object appear lighter; an involuntary contraction of the antagonists makes it appear heavier. If the involuntary contraction of the agonists is strong enough, a peculiar sensation of lightness, a kind of "negative weight," is experienced. (*c*) The sensation of heaviness and lightness due to involuntary changes of contraction of the muscles may be accompanied by further subjective phenomena: With the sensation of heaviness may be associated the impression of a slight shortening of the limb in question, and with the sensation of lightness there may be a marked impression of elongation of the limb, or of the whole body, or an impression as if a light, airy substance were passing through the limb and emanating from it. All these phenomena can be elicited experimentally in normal subjects (experiments of Ponzo).

A case is reported which illustrates clearly the somatic sensations discussed. The outstanding feature in the psychopathologic picture of the patient is profound disturbances of self-awareness. The psychologic experiences of the patient have partly lost their usual relation to the ego: He feels that parts of his body, his thoughts and his feelings do not belong to his ego but are things foreign to him.

Analogous disturbances are to be observed in regard to the psychomotor activity. The patient's actions have partly lost their usual relation to the ego. They are excluded from the self and appear to the patient not as his own actions but as something "done" to him. The muscular activities or tendencies to such activities generate changes in the muscle tonus, which, because they have lost their ego-reference, are psychologically accounted for as foreign forces acting on the body. One may expect, therefore, that in such patients will appear spontaneously all the phenomena which can be observed when one experimentally induces an involuntary contraction of the muscle in a normal subject (sensations of heaviness and of lightness, etc.).

The somatic complaints of the patient are described and analyzed. A sensation of lightness of the body, sometimes accompanied by the sensation of flying, a sensation of heaviness of the body, sensations as if the body were expanding or shrinking and an impression of an airy substance passing through the muscles and emanating from the body

are reported. Analysis of these symptoms clearly indicates their origin in muscular activities which have become disconnected from the ego.

A group of somatic complaints which represent modifications of the postural model of the body are discussed. They are: impairment of the unity of the body, impairment of the continuity of the body, an impression of emptiness of the inside of the body (the latter in some instances explains the negativistic attitude toward the intake of food and the ravenous appetite of schizophrenic patients), a reduction of the dimensions of the body, impairment of orientation on one's body, an impression of displacement of parts of the body, a disturbance of the experience of space and an impression of lifelessness of parts of the body. Many of the latter phenomena are also definitely related to unusual muscle sensations but probably are not completely reducible to them.

Disturbances of the postural model of the body similar to the phenomena discussed in this paper have been described in cases of certain types of lesion of the brain. They also have been reproduced experimentally. The cortical tissue along the interparietal sulcus, the gyrus angularis, the posterior part of the gyrus supramarginalis and the sensory visual band of Elliot Smith seem to be the most important regions for postural recognition and associated functions. The neurologic observations and the results of special tests suggested that in the case reported some neurologic involvement, possibly in the parietal lobe, may be present, but the objective findings were not sufficiently clearcut to allow a further conclusion.

As previously stated, certain somatic complaints of schizophrenic patients are based on definite muscle sensations caused by changes of muscle contraction which have lost their usual relation to the ego. The loss of ego-reference of muscular activity is a manifestation of a more general disturbance of self-awareness. The latter is not further analyzed in this paper but is taken as a descriptive fact. From the psychologic point of view, the loss of ego-reference seems to represent a special kind of defense mechanism.

EXPERIMENTAL STUDIES ON HEADACHE

OBSERVATIONS ON HEADACHE PRODUCED BY HISTAMINE

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The purpose of this communication is to present evidence concerning one mechanism of headache. The data demonstrate how under the given experimental conditions headache is produced and indicate the sites of origin of the nerve impulses which are interpreted as pain.

It is generally agreed that most of the intracranial contents, including the brain substance and large portions of the meninges, are not the sites of origin of painful sensations.[1] However, the more recent reports of many neurosurgeons, including Craig,[1a] Elsberg,[1c] Fay,[1d] Foerster [2] and Penfield,[1g] indicate that the large dural vessels, notably the arteries and possibly the dura itself in the neighborhood of these vessels, are regions from which a sensation of pain can be produced by adequate stimulation. To these Penfield [1g] added the venous sinuses of the dura.

Fay [1d] has initiated painful sensations by stimulation of the larger arteries of the pia near the base. This finding is supported by the

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1. (*a*) Craig, W. M.: Localized Headaches Associated with Lesions of Meningeal Vessels, J. A. M. A. **100**:816 (March 18) 1933. (*b*) Cushing, H., in Keen, W. W.: Surgery, Its Principle and Practice, Philadelphia, W. B. Saunders Company, 1911, vol. 3, p. 223. (*c*) Elsberg, C. A.: The Relation of Variations in Intraventricular and Intracranial Pressure to Headache, A. Research Nerv. & Ment. Dis., Proc. **8**:3, 1929. (*d*) Fay, T.: Certain Fundamental Cerebral Signs and Symptoms and Their Response to Dehydration, Arch. Neurol. & Psychiat. **26**:452 (Aug.) 1931. (*e*) Lennander, K. G.: Ueber lokale Anästhesie und über Sensibilität in Organ und Gewebe, weitere Beobachtungen: II., Mitt. a. d. Grenzgeb. d. Med. u. Chir. **15**:465, 1906. (*f*) Levine, M., and Wolff, H. G.: Cerebral Circulation: Afferent Impulses from the Blood Vessels of the Pia, Arch. Neurol. & Psychiat. **28**:140 (July) 1932. (*g*) Penfield, W.: A Contribution to the Mechanism of Intracranial Pain, A. Research Nerv. & Ment. Dis., Proc. **15**:399, 1934. (*h*) Pickering, G. W.: Observations on the Mechanism of Headache Produced by Histamine, Clin. Sc. **1**:77, 1933.

2. Foerster, O.: Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände, Beitr. z. klin. Chir. **30**:308, 1927.

experimental work of Hitz and Kammer [3] and the later work of Levine and Wolff,[1f] who found that stimulation of the larger pial arteries and the surrounding pia of the cat with faradic current caused changes in the galvanic responses of the skin while no such changes were obtained from other parts of the pia. The existence of such reflex phenomena made it seem likely that afferent impulses arose from the stimulated blood vessels of the pia. Since this type of response is elicited chiefly by painful stimuli, it was inferred that the large pial arteries, when adequately stimulated, can give rise to painful sensations. The accumulated evidence, therefore, points to the blood vessels of the meninges, both the dural and the larger pial vessels, as potential sites of painful sensations within the intracranial cavity.

It is reasonable to infer, then, that the blood vessels and the headache may be related. Faradization, pulling and clamping of the intracranial blood vessels have already revealed that these are sensitive structures, but the part played by these vessels in the headache commonly experienced by man cannot be established by such grossly artificial means.

To ascertain experimentally the rôle of the blood vessels in headache the agent used to produce pain must not only regularly produce headache in man but must be otherwise completely innocuous; its effects must be short-lived and at least one component of its action measurable. Histamine fulfils these requirements, since its effects on the intracranial blood pressure are predictable, the induced headache is equally predictable, and its effect on the blood pressure and the cerebrospinal fluid pressure is measurable. Pickering [1h] has used histamine in the production of experimental headache, and his observations indicate that the action of the drug on the intracranial vessels and the resultant headache are related.

The headache that follows a single injection of histamine lasts from one and one-half to five minutes and leaves no sequelae. In addition to headache, histamine also causes cerebral as well as general arterial vasodilatation (Forbes, Wolff and Cobb [4] and Weiss [5] and others).

3. Hitz, J. B., and Kammer, A. G.: The Effects of Stimulation of Cerebral Blood Vessels, Thesis, University of Wisconsin, 1926, quoted by Leake, C. D.; Loevenhart, A. S., and Muehlberger, C. W.: Dilatation of Cerebral Blood Vessels as a Factor in Headache, J. A. M. A. **88**:1076 (April 2) 1927.

4. Forbes, H. S.; Wolff, H. G., and Cobb, S.: The Cerebral Circulation: X. The Action of Histamine, Am. J. Physiol. **89**:266, 1929.

5. (*a*) Weiss, S., and Lennox, W. G.: The Cerebral Circulation: XVII. The Cerebral Blood Flow and the Vasomotor Response of the Minute Vessels of the Human Brain to Histamine, Arch. Neurol. & Psychiat. **26**:737 (Oct.) 1931. (*b*) Weiss, S.; Robb, G. P., and Ellis, L. B.: The Systemic Effects of Histamine in Man, with Special Reference to the Responses of the Cardiovascular System, Arch. Int. Med. **49**:360 (Feb.) 1932.

The general vasodilatation produced in man by the doses of histamine used in our experiments and in those of Pickering [1h] is accompanied consistently by a sharp drop of from 10 to 40 mm. in the systolic and diastolic arterial pressure, coming about from twenty to twenty-five seconds after the injection of the drug, and by a simultaneous sharp rise in intracranial pressure,[6] which is due to the increased vascular bed. At about the same time the subject notices a metallic taste. The arterial pressure remains lowered for from twenty to thirty seconds, then starts to return to the normal or a slightly higher level with a closely concomitant reduction in the cerebrospinal fluid pressure (fig. 5).

Forbes, Wolff and Cobb [4] found that an analogous series of events takes place in the cat. They observed in addition that the dilatation of the cerebral vessels continues for a short time after the arterial pressure has begun to return. This indicates that the cerebral flow is probably greatest when the systemic arterial pressure has ascended to normal after its initial drop. Schmidt [7] and Wolff and Cattell [8] have recently measured the cerebral blood flow by means of a thermocouple in the cat's brain and have ascertained that the cerebral blood flow is indeed greatest at this time. They observed that immediately after the injection of histamine the systemic arterial blood pressure and the cerebral blood flow both fell slowly; shortly after the blood pressure began to mount again, the cerebral blood flow began to rise, and before the systemic pressure had returned to the preinjection level, the cerebral flow far exceeded its original amount. It remained for some time at this high level before returning to the preinjection rate. Schneider,[9] using a thermostromuhr in the internal carotid artery, observed similar effects after injection of histamine. Furthermore, it has been observed that after injection of histamine [10] there is an increase in the amplitude of the intracranial pulsations. If this increase represents an increased effect of cardiac systole on dilated cerebral arterial walls, then simultaneous measurement of cerebral blood flow and amplitude of intracranial pulsations should show a relationship. In other words, after the injection of histamine there should be first a decreased cerebral blood flow with but slight change in the amplitude of pulsation, followed

6. Pickering.[1h] Forbes, Wolff and Cobb.[4]

7. Schmidt, C. F.: The Intrinsic Regulation of the Circulation in the Hypothalamus of the Cat, Am. J. Physiol. **110**:137, 1934.

8. Wolff, H. G., and Cattell, M.: To be published.

9. Schneider, M., and Schneider, D.: Untersuchungen über die Regulierung der Gehirndurchblutung: II. Mitteilung. Einwirkungverschiedener Pharmaca auf die Gehirndurchblutung, Arch. f. exper. Path. u. Pharmacol. **175**:640, 1934.

10. Pickering.[1h] Weiss, Robb and Ellis.[5b]

by an increased cerebral blood flow and a great increase in the amplitude of the intracranial pulsations. Preliminary experiments on cats demonstrated this relationship.

A needle inserted into the cisterna magna was connected with a Frank capsule. Moving bromide paper in a camera recorded the waves made by a beam of light reflected from the capsule. Through a hole in the parietal portion of the skull a thermocouple was submerged beneath the surface of the brain. A stopper snugly fitting about the connections of the thermocouple sealed the hole in the skull.

It was observed that shortly after the injection of histamine and coincident with the fall in systemic arterial blood pressure there was a decrease in cerebral blood flow with but little change or a slight fall in the amplitude of the intracranial pulsations. However, with the restoration of the blood pressure there was an increase in cerebral blood flow. Moreover, the amplitude of the intracranial pulsations considerably exceeded their original height.

It may be concluded, therefore, that the increased amplitude of intracranial pulsations after injections of histamine actually represents an increase in stretch of dilated intracranial vessels with each cardiac systole, and that dilatation itself is not sufficient to increase the amplitude and blood flow if there is at the same time a fall in blood pressure. However, vasodilatation plus a normal systemic arterial pressure will cause both increased cerebral blood flow and increased amplitude of intracranial pulsations. Thus in the case of histamine there is demonstrated a relationship between the cerebral blood flow, systemic arterial blood pressure and amplitude of the intracranial pulsations. These considerations become particularly significant when it is recalled that the dural vessels, the dural sinuses and the larger pial vessels are important pain-sensitive structures.

Since the increase in amplitude of intracranial pulsations is an expression of changes in pressure in the intracranial and intraspinal arteries, it seemed reasonable to use it as a means of studying the relation of cerebral vessels to headache produced by an experimental agent such as histamine. Information about this relationship has been obtained in human experiments in which, by means of a needle in the lumbar sac, the amplitude of the intracranial pulsations was ascertained and its relation to headache produced by histamine analyzed in the following manner.

METHOD

The subjects of these observations were patients on whom it was necessary to perform lumbar puncture for diagnostic purposes and several healthy volunteer adults. The results in the former differed in no wise from those in the latter. With the subject lying on his left side (fig. 1) a lumbar puncture was made and the needle connected with a Frank capsule (*B*) by means of a column of sterile physiologic solution of sodium chloride contained in metal and heavy rubber tubing. For comparison and in order to obtain a record of actual changes

in arterial pulsations, simultaneous photographs were taken of the changes in the pulsations in the temporal artery. For this purpose another Frank capsule (*A*) was connected with a tambour on the temporal pulse by an air system. The two capsules were arranged so as to reflect horizontal beams of light into the camera which contained a moving strip of bromide paper. In this way changes in pressure within the subarachnoid space were recorded simultaneously with changes in the amplitude of the temporal pulse. Cerebrospinal fluid pressure was taken frequently by a manometer which could be connected or disconnected from the system by a stopcock. A device recording time at one-fifth second intervals also made a record directly on the moving paper. Readings for blood

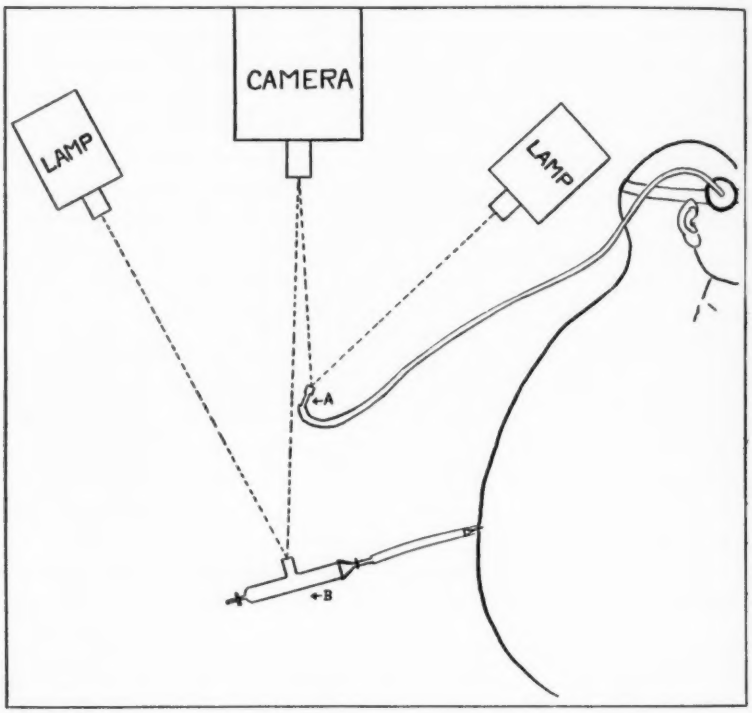

Fig. 1.—Diagram of the arrangement of the subject and the apparatus for registering, by means of light beams reflected from two Frank capsules, the temporal pulse (*A*) and the pulsations in the subarachnoid space (*B*) representing intracranial and spinal arterial pulsations and briefly referred to here as "intracranial pulsations."

pressure were made at frequent intervals by the auscultatory method with the sphygmomanometer on the right arm.

The camera was started and a record taken of the resting stage in each subject. One-tenth cubic centimeter of a 1:1,000 solution of histamine acid phosphate was then injected into the median basilic vein of the left arm. The exact moment of the injection as well as the moment of each reading of the blood pressure and each sensation experienced by the subject was signaled directly on the photographic

record by tapping the time recorder. The camera was run continuously from the initial resting stage through the administration of the injection and the beginning of the headache and until the headache had completely disappeared. The recorded pulsations representing the changes in pressure in the subarachnoid space produced by intracranial and intraspinal pulsations will, for the sake of brevity, be referred to throughout as "intracranial pulsations."

In nineteen subjects the effects of the injection of histamine were investigated. Sixteen technically satisfactory experiments were obtained on eleven subjects, and fourteen technically satisfactory single injections of histamine in nine subjects. One subject on whom a technically satisfactory experiment was made was very suggestible, and the results were therefore waived. Two subjects were given repeated injections of histamine in rapid succession. Only one of these experiments was technically satisfactory. One subject received a continuous infusion of histamine. In two subjects, inhalation of carbon dioxide was studied as well as injection of histamine.

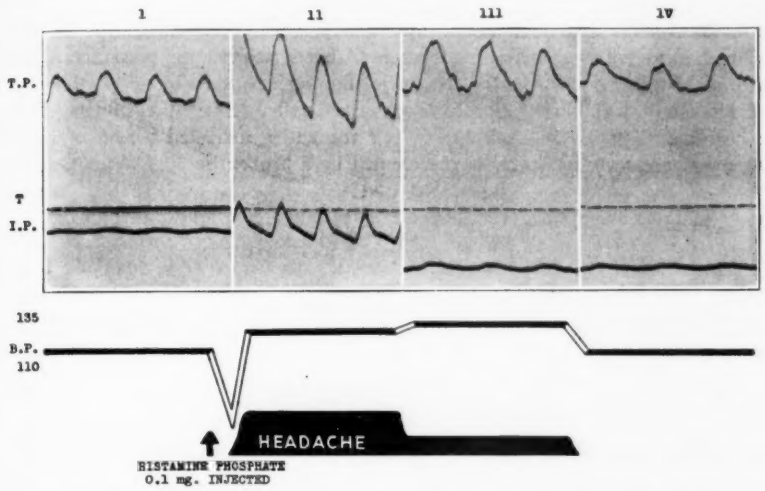

Fig. 2.—Representative sections from a photographic record of the temporal pulse and intracranial pulsations during headache produced by histamine in subject C., with the duration of the headache, the variations in blood pressure and the injection of histamine indicated diagrammatically. In this and the succeeding figures *T.P.* represents temporal pulse; *I.P.*, intracranial pulsations; *T*, time in 0.2 second intervals; *B.P.*, blood pressure (systolic).

Figure 2 (subject C) shows a series of sections taken from the record of a typical experiment. In I the temporal pulsations and the intracranial pulsations as recorded from the pulsatile expansions in the lumbar arachnoid space are minimal in the resting stage; in II the intracranial and temporal pulsations are at their greatest amplitude and the headache is maximal, while the arterial pressure after a fall has returned to slightly above the original resting level; in III the brain and temporal pulses are subsiding and the headache is growing less intense, while the arterial pressure remains at about the same level; in IV the pulsations are once more minimal and the headache has entirely disappeared. Figure 3 (subject S) and figure 4 (subject R. R.) illustrate similar experiments.

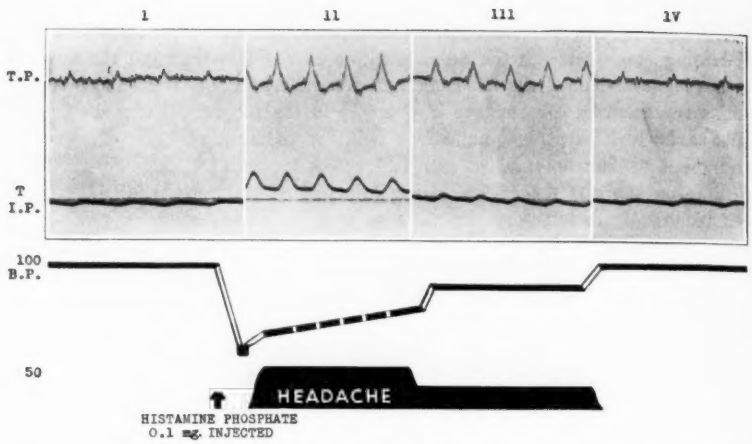

Fig. 3.—Representative sections from a photographic record of the temporal pulse and intracranial pulsations during headache produced by histamine in subject S., with the duration of the headache, the variations in blood pressure, and the injection of histamine indicated diagrammatically. Since the subject in this case complained of severe headache during the entire indicated period of rapidly rising blood pressure, the latter is represented by a broken line. The photographic sections of the intracranial pulsations and the temporal pulse are at a point midway in the broken line.

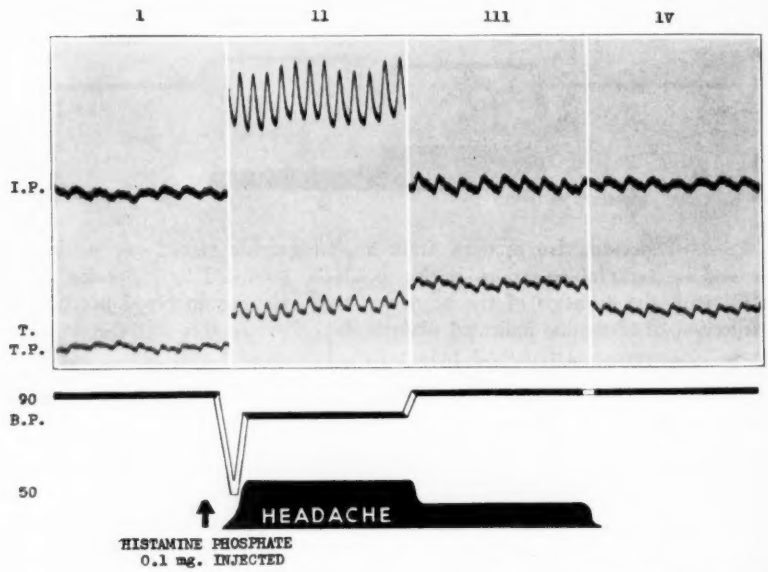

Fig. 4.—Representative sections from a photographic record of the temporal pulse and intracranial pulsations during headache produced by histamine in subject R. R., with the duration of the headache, the variations in blood pressure, and the injection of histamine indicated diagrammatically. The time was recorded in this instance on the same line as the temporal pulse.

Figure 5 (subject G) is a diagrammatic representation of the course of events throughout such an experiment. The results of all the experiments are in accord although the changes are not always of the same degree as in the one illustrated here.

Thirteen technically satisfactory experiments were performed on eight subjects. There are six groups of measurements: the first represents the resting level of the blood pressure, the amplitude of the intracranial pulsations, the amplitude of the temporal pulse and the rate of pulsation; the second group was made at the point marked on the record when, after the injection of histamine, the subject first noticed the characteristic metallic taste; the third group was made when headache began, the fourth when the headache was severe, the fifth when the headache was going, and the sixth when the headache was gone.

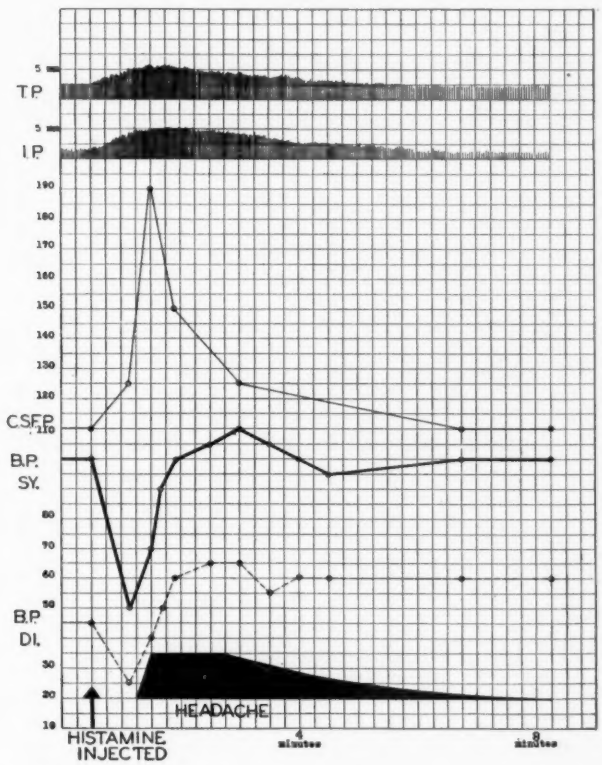

Fig. 5.—Diagrammatic representation of the course of events during headache produced by histamine in subject G. The headache was most severe with rising blood pressure, and it should be noted that at this time the cerebrospinal fluid pressure is returning to its resting level from the high point reached after the injection of histamine. Increase in amplitude and rate of the temporal pulse (*T.P.*) and of the intracranial pulsation (*I.P.*) are indicated in the upper two shaded areas. The line *C.S.F.P.* indicates the cerebrospinal fluid pressure in millimeters of Ringer's solution. Systolic blood pressure is indicated by the heavy black line at *B.P. SY.*, and the diastolic blood pressure is indicated by the broken line at *DI.*

The measurements of the amplitude of intracranial pulsations on the various subjects are not directly comparable with each other, for in each instance a different membrane was used on the Frank capsule and there was also considerable difference between subjects in the degree of success achieved in obtaining a free flow of cerebrospinal fluid into the system. In any one subject, however, condi-

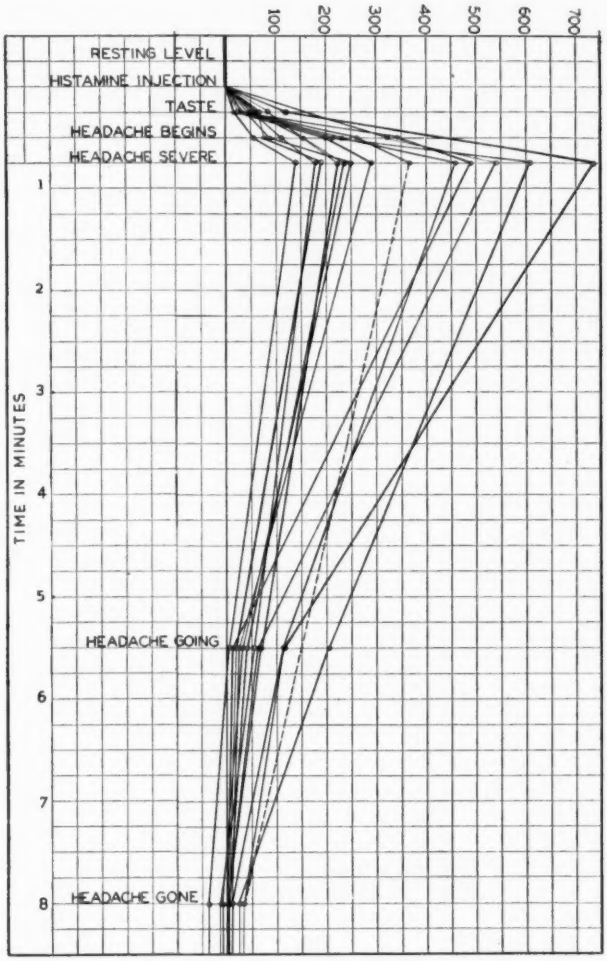

Fig. 6.—Graphic representation of the percentage increase in the amplitude of the intracranial pulsations during headache produced by histamine in each of thirteen experiments. Since the times of onset of metallic taste, of the beginning of headache, etc., in the thirteen experiments closely approximated each other, the average time was plotted.

tions remained unchanged throughout a given experiment so that changes in amplitude of "intracranial pulsations" truly represent changes in pressure within the lumbar sac. Figure 6 shows graphically the percentage changes in amplitude

of the intracranial pulsations in each of the thirteen experiments. It will readily be seen that the trend of all the graphs is much the same although there are wide variations from subject to subject in the exact position of the points. In every instance the amplitude of the intracranial pulsations closely follows the intensity of the headache, and the increase in both will be noted to occur as the changes in blood pressure and intracranial pressure subside. The latter observations were also made by Pickering.[1h] After the injection of histamine the blood pressure fell sharply; it began to return to normal with the onset of the pain in the head. The amplitude of intracranial pulsations was increased as soon as the subject reported "taste." The amplitude of the oscillations was increased still more as headache was beginning and reached its maximum when the headache was most severe. After this it receded gradually to the initial resting level, at which point the headache had disappeared.

The increase of temporal and intracranial pulsations was of a different magnitude in the patients studied. Thus subject C had an increase of intracranial pulsation of 547 per cent, whereas the temporal pulsation was increased 100 per cent (table [11]).

In figure 7 (subject F) are shown the results of continuous infusion of histamine. At I is shown the height of the intracranial pulsations before injection of histamine while at II and III are seen the pulsations after the infusion of histamine has started (0.1 mg. of histamine acid phosphate per minute). It is to be noted that the amplitude of the intracranial pulsations is but slightly increased during the period of infusion of histamine; the blood pressure falls and continues at a low level. The small intracranial pulsations and low blood pressure continue as long as the intravenous infusion persists. At IV, with the cessation of the infusion and the rise in blood pressure, the intracranial pulsations increase in magnitude and the headache begins. It reaches its maximum at V and persists for the usual length of time after histamine has been injected. At VI the headache is disappearing; at VII it is gone.

Great increase in intracranial pressure played no part in the production of the headache following injection of histamine. In fact, the pressure of the cerebrospinal fluid was in no case elevated to more than 300 mm. of water, and the peak pressure usually occurred from ten to twenty seconds before the onset of the headache. When the headache was of maximum intensity and the intracranial pulsations were maximal, the cerebrospinal fluid pressure was falling toward the resting level or had reached it. Pickering [1h] made similar observations and inferences.

The effect of increased intracranial pressure on the headache produced by histamine was ascertained in four experiments on one of the nineteen subjects by the procedure of raising the cerebrospinal fluid pressure to 500 or 600 mm. of water by injection of physiologic solution of sodium chloride into the lumbar arachnoid space. Pickering's observation [1h] that the headache was relieved by this procedure was confirmed, but the relation of the improvement to the amplitude of the intracranial pulsations could not be satisfactorily determined with our technic.

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11. Clark, Dean; Hough, Heloise, and Wolff, H. G.: Experimental Studies on Headache: Observations on Headache Produced by Histamine, in Pain: Its Mechanisms and Disturbances, Association for Research in Nervous and Mental Diseases, Baltimore, The Waverly Press, 1935, vol. 15, p. 417.

In three of the nineteen subjects there was ascertained the effect of another important cerebral vasodilator which seldom produces headache, namely, carbon dioxide. In one subject, the change in the height of the amplitude of the intracranial pulsations after breathing 5 per cent carbon dioxide and 95 per cent oxygen was in one instance from 3.3 to 4.4 mm. (+33 per cent) and in another from 2.9 to 4.6 mm. (+57 per cent). There was a sensation of fulness in the head but not true headache or pain. On this same subject, however, histamine produced an increase of amplitude of 100 per cent and at this point definite (although moderate) headache was experienced. With the administration of 10 per cent carbon dioxide and 90 per cent oxygen, the change in the magnitude of the intracranial pulsations was in the other subject from 3.9 to 9.3 mm. (+141 per cent), in

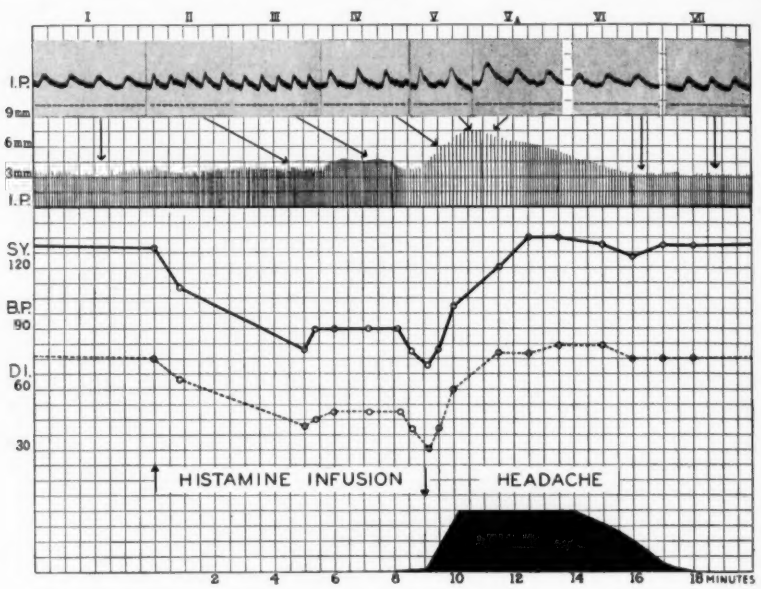

Fig. 7.—Diagrammatic and photographic representation of the course of events in the experiment in which histamine acid phosphate (0.1 mg. per minute) was infused continuously during nine minutes. Systolic blood pressure is indicated by the heavy black line *SY.* and diastolic pressure by the broken line *DI.* At *I.P.* the variations in rate and amplitude of the intracranial pulsation are represented and the top line *I.P.* is made up of approximately corresponding sections from the photographic record of the intracranial pulsation. Arrows point from the photographed intracranial pulsation to the corresponding pulsation represented diagrammatically. It should be noted that the slow rate of pulsation during the height of the headache and at the maximum amplitude of oscillation is exceptional to this case. The pulse rate is usually more rapid during the height of the headache.

another from 3.4 to 9.4 mm. (+170 per cent), in a third from 3.9 to 10.3 mm. (+164 per cent). The feeling of fulness in the head was more pronounced, but headache was not experienced. Histamine was not used on this subject.

Clearly the threshold for headache in the first subject (who experienced headache with an increase of 100 per cent) was much lower than that in the second (who had no headache with an increase of 170 per cent). But of paramount importance is the fact that headache did not occur in the first subject with an increase of 57 per cent carbon dioxide but did occur when the increase reached 100 per cent (histamine).

COMMENT

The results reported demonstrate that the intensity of the headache produced by histamine is proportional to the degree of dilatation and stretch of the intracranial vessels and the perivascular tissue. The evidence at hand does not indicate that stretch of the meninges as the result of great increase in intracranial pressure was an important factor in the production of the headache. Pickering [1h] drew similar inferences from his own experiments and supported this view by showing that raising the arterial pressure or lowering the cerebrospinal fluid pressure during the headache intensified the pain. Conversely, lowering arterial pressure or raising cerebrospinal fluid pressure decreased it; these facts of observation were confirmed by us.

The following explanation of these effects is offered. During the usual state of contraction of the walls of intracranial blood vessels, cardiac systole is reflected as a minor change in the intracranial pressure: the elastic contracted muscle resists pressure changes and absorbs the impact. It has been shown [12] in other vascular beds and can be postulated here that under these circumstances a certain number of afferent impulses arise from the vessel walls with each systole. When, however, as after injection of histamine, the vessels are distended, the number of impulses arising from their walls is greatly increased [12] and is accentuated with each systole. Moreover, the ability of the now hypotonic walls of the vessels to absorb changes in pressure is much reduced and the variations in pressure within the vessels are thus more directly transmitted to sensory end-organs in and about their walls and to the subarachnoid space. The resulting unusual flood of afferent impulses is interpreted as pain.

The experiments on which this explanation is based are as follows: The effect of histamine on the cerebral vessels as determined by actual measurement is such that their diameters are commonly increased between 40 and 50 per cent.[4] Dural vessels also participate in the dilatation.[13] It is reasonable to infer that such great changes in diameter indicate a loss of tone which interferes with the ability of the wall of the vessel to absorb any but minimal changes in intravascular

12. Bronk, D. W.: The Nervous Mechanism of Cardio-Vascular Control, The Harvey Lectures, Baltimore, Williams & Wilkins Company, 1935, p. 245.

13. Pool, J. Lawrence: Personal communication.

pressure. Consequently the sensory end-organs in and about the walls of the vessels are subjected to intense stimulation by the cardiac impulses.

If the strain on the wall of the dilated vessel is relieved by lending support from without, for example, by raising the cerebrospinal fluid pressure, there is improvement in the headache even though there is slight or no reduction in the actual diameter of the vessel. Improvement in the headache followed elevation of the cerebrospinal fluid pressure to 500 or 600 mm. of water. Pressure much higher than this brings new factors [14] into play, such as direct stretch of the meninges and dilatation of the cerebral ventricles. This produces headache but of a different type, the nature of which has no place in this discussion.

The height of the oscillations of the intracranial pulse is reduced and the headache produced by histamine relieved in a different way by reduction of the systemic arterial pressure. In this case the intramural pressure is reduced and the intracranial vessels, although dilated, are not stretched as much. This explanation of the improvement in headache is supported by experiments done by Wolff and Cattell [8] on the cat. When the cerebral blood flow was at its height following injection of histamine, it was found that a lowering of the arterial pressure (by increasing the intrathoracic pressure) produced a prompt decrease in the cerebral blood flow in spite of the action of histamine.

The fact that headache, height of the intracranial pulsations and level of the systemic arterial blood pressure are intimately related is clearly demonstrated in our confirmation of Pickering's experiment [1b] in which histamine was continuously infused. During the period of lowered blood pressure the amount of histamine in the blood stream is as great as, if not greater than, that during any other period, but no headache is experienced. From this we infer, in agreement with Pickering, that the presence of histamine does not in itself cause headache. An explanation of these results is given by another experiment of Wolff and Cattell.[8] It was found that during slow intravenous infusion of histamine in cats the systemic arterial pressure remained at a low level as long as the infusion continued. During the period of lowered blood pressure the cerebral blood flow was less than at the initial level. When the infusion stopped the arterial pressure promptly returned to its original level or one somewhat higher. At the same time the cerebral blood flow increased rapidly and soon reached a level

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14. Elsberg.[1c] Wolff, H. G., and Forbes, H. S.: The Cerebral Circulation: V. Observations of the Pial Circulation During Changes in Intracranial Pressure, Arch. Neurol. & Psychiat. **20**:1035 (Nov.) 1928. Fay, T.: The Treatment of Acute and Chronic Cases of Cerebral Trauma by Methods of Dehydration, Ann. Surg. **101**:76, 1935.

considerably higher than it was before the infusion of histamine, even before the arterial pressure ascended to its original level.

Pickering [1h] observed that if after injection of histamine a second injection is given at the height of the headache the latter promptly disappears, to return sometime later when the second injection of histamine takes effect. This experiment was repeated in three of the aforementioned nineteen human subjects. The headache and the amplitude of the intracranial pulsations diminished with the second injection, although no definite conclusions concerning the effect on intracranial pulsations in their relation to the improvement could be drawn. It seemed probable, however, that the observed reduction in amplitude of oscillations when the headache disappeared was due to the second injection.

A similar phenomenon was observed by Wolff and Cattell.[8] If one injection of histamine was followed by a second, given just before the systemic arterial blood pressure had regained its original level, the increase in cerebral blood flow that usually accompanied this phase of the action of histamine was promptly overcome or did not occur. In fact, the cerebral blood flow was again slowed and reached the low level at which it had been shortly after the first injection. This effect could be repeated, for if, as the blood pressure again approached normal, histamine was injected for the third time, the blood pressure fell and again the cerebral circulation was slowed. In other words, the vasodilative action of histamine is without effect in increasing the cerebral blood flow until the systemic pressure has started definitely to return to its original level. It is precisely at this point that the headache in man is most severe (Pickering [1h]). These findings lend support to the previously stated formulation that headache produced by histamine results from the stretch of the walls of the intracranial vessels during the period in which they are hypotonic and unable adequately to absorb the shock of the systemic arterial pressure.

The effects of carbon dioxide described indicate that headache does not occur unless the intracranial vessels are sufficiently distorted. In a few subjects in whom histamine produced lesser changes in the amplitude of oscillation, no headache or only a mild one was produced. The difference in amplitude of the oscillations produced by histamine and carbon dioxide is in accordance with the observations on the diameter of the pial vessels made by direct measurements in cats. Histamine commonly caused a change in diameter of over 50 per cent;[4] carbon dioxide seldom more than 30 per cent.[15] In general it may be said that in man there are undoubtedly large differences between individual sub-

15. Wolff, H. G., and Lennox, W. G.: Cerebral Circulation: XII. The Effect on Pial Vessels of Variations in the Oxygen and Carbon Dioxide Content of the Blood, Arch. Neurol. & Psychiat. **23**:1097 (June) 1930.

jects and in the same person at different times in the threshold at which pain is experienced. Nevertheless, headache of the type observed in these experiments occurs only when the amplitude of the intracranial pulsations increases to a degree more striking than that seen in the same person with a vasodilator which does not produce headache, such as carbon dioxide.

It is conceivable that the increased blood flow which is an accompaniment of the cerebral vasodilatation following injection of histamine is, by virtue of its effect in dilating the sensitive venous sinuses, really the cause of the headache. This may be an additional factor, but it seems unlikely that it is the chief factor. In our experience and also in that of Pickering,[1h] jugular compression in many instances caused the headache to diminish or disappear. This could hardly occur if the headache were the result of engorgement of the venous sinus since, were this the case, jugular compression with venous stasis would actually augment it.

To recapitulate, the postulate is presented that the headache following the injection of histamine is the result of a discrepancy between the behavior of the blood vessels inside the head as compared with those elsewhere. The rise of the systemic blood pressure after its fall indicates that at least a portion of the total vascular bed is constricting. However, the cerebral vessels remain dilated for a short time,[4] and the cerebral blood flow is increased. In fact, with the rise in systemic blood pressure the cerebral arteries are still further dilated and bear the brunt of heightened intramural pressure with each cardiac systole. Moreover, the ability of the now hypotonic walls of the vessels to absorb pressure changes is much reduced and the pressure variations within the vessels are thus more directly transmitted to sensory end-organs in and about their walls and to the subarachnoid space. It is suggested that the combination of these two factors causes headache through the stretching effects on the walls and perivascular tissues of the larger dural and pial vessels, chiefly the arteries. The walls of these vessels are the sites of origin of the afferent impulses interpreted as pain.

Headaches similar in mechanism to those following injection of histamine and like them probably dependent on intracranial vascular effects are produced by such vasodilators as amyl nitrite,[16] carbon monoxide and foreign proteins.[17] It is likely that there are other exogenous and endogenous agents that act in the same way.

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16. Wolff, H. G.: The Cerebral Circulation: XIa. The Action of Acetylcholine. XIb. The Action of the Extract of the Posterior Lobe of the Pituitary Gland. XIc. The Action of Amyl Nitrite, Arch. Neurol. & Psychiat. **22**:686 (Oct.) 1929.

17. Wolff, H. G. P., in Piersol, G. M.: Section on Cerebral Circulation, in the Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, 1933, vol. 3, p. 250.

SUMMARY

The association of headache following the injection of histamine with increase in the amplitude of the intracranial pulsations was photographically demonstrated. Simultaneous records of the systemic arterial blood pressure, the cerebrospinal fluid pressure, the temporal arterial pulsations and the intracranial pulsations were made.

The demonstrated correlation is taken as further evidence that the headache produced by histamine is primarily due to dilatation and stretch of the pial and dural arteries and their surrounding tissues.

The extent to which this mechanism affords an explanation for nonexperimental headache is suggested.

Miss Helen Goodell assisted in the experiments and in the preparation of the manuscript.

Case Reports

PAROXYSMAL NEURALGIA OF THE TYMPANIC BRANCH OF THE GLOSSOPHARYNGEAL NERVE

Report of a Case in Which Relief Was Obtained by Intracranial Section of the Glossopharyngeal Nerve

THEODORE C. ERICKSON, M.D., MONTREAL, CANADA

Glossopharyngeal neuralgia is a definite clinical entity. The disease is rare, and the possible clinical variants are not as well understood as they are in cases of trigeminal neuralgia. In its sudden brief painful paroxysms, in the complete relief afforded by section of the posterior root and in the obscure etiology, it resembles tic douloureux of the fifth nerve. The pain of trigeminal neuralgia may originate in any of the peripheral branches of any of the three sensory divisions of the nerve. A priori, it is reasonable to suppose that the same phenomenon may be expected in glossopharyngeal neuralgia, and it does occur. The justification for reporting the following case is the fact that it is an example of paroxysmal neuralgia originating in the tympanic branch of the glossopharyngeal nerve; the trigger zone initiating the pain was probably within the eustachian tube, and complete relief followed intracranial section of the ninth nerve.

REPORT OF CASE

Mrs. I. B., aged 62, was referred to the clinic by Dr. H. S. Birkett, of Montreal, because of severe paroxysmal attacks of pain below the left ear just posterior to the angle of the mandible. The past and the family history were irrelevant. The patient had been entirely well until 1930, when she awoke one night with severe steady pain over the left side of the head and stiffness of the neck. This lasted for two weeks and then disappeared, never to recur. For one year she seemed entirely well, and then she began to have periodic attacks of pain localized to the left side, starting below the external auditory meatus and radiating to a point just in front of it and deep in the neck. The pain felt at times as though a knife had been stuck deep in the ear. The paroxysms of pain lasted from fifteen to thirty seconds. There were three or four a day for one week and then a period of freedom for three months. When the pain returned after the free interval, it became very much more frequent and more intense. It came on spontaneously. Swallowing, talking, laughing, sneezing and blowing the nose precipitated it. During the paroxysm she would bring both hands to the face and remain motionless for from fifteen to thirty seconds until the pain ceased. General physical examination

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gave essentially normal results. Analysis of blood and urine disclosed nothing of note. Except for a slight deviation of the uvula to the right and an equivocal diminution of the pharyngeal reflex on the left, neurologic examination revealed nothing abnormal. Otolaryngologic examination was made repeatedly and nothing organically abnormal was found.

Special Clinical Studies.—Cocainization of the Pharynx, Palate, Tonsils and Posterior Third of the Tongue: On repeated occasions over a three year period complete anesthetization of the pharynx, nasopharynx, tonsils and posterior third of the tongue was carried out. She would never admit that the pain was influenced as to its distribution or its intensity during the period over which anesthesia persisted. Although the impression had been that she had glossopharyngeal neuralgia, the lack of relief following cocainization threw considerable doubt on the diagnosis.

Attempts to Demonstrate a Trigger Zone: Stimulation of the palate, tonsillar fossa, posterior third of the tongue and external auditory canal did not induce the pain. The only portion of the sensory distribution of the glossopharyngeal nerve which was not tested directly was that to the eustachian tube and the middle ear. The pain was frequently initiated when the patient swallowed on command.

Injection of Alcohol into the Left Mandibular Nerve at the Foramen Ovale: Driven almost to distraction by the severity and frequency of the attacks of pain, the patient became greatly discouraged and an unreliable witness of her symptoms. It was concluded that alcoholic block of the third division of the fifth nerve rather than procainization was advisable so that a sufficiently long period of anesthesia would be present to permit definite conclusions to be drawn as to the effect on the pain. As a result complete anesthesia of the left third division was produced, i. e., the anterior two thirds of the tongue, the lower lip and a band extending from the lower lip up to the scalp and including the anterior part of the external auditory canal. The pain, however, continued unchanged.

Parotid Secretion: Observations made on the secretion of the parotid gland both by direct inspection and by the method of Poth[1a] showed no difference in secretion of the parotid gland on the two sides even during the paroxysms of pain. From the right the secretion was 0.655 Gm., and from the left it measured 0.565 Gm., over a three minute period.

Intracranial Section of the Left Glossopharyngeal Nerve: Intracranial section of the left glossopharyngeal nerve was performed on Nov. 28, 1934, under avertin-ether anesthesia by Dr. William Cone.

Postoperative Results and Investigations: From the day of operation up to the date of the last examination (Dec. 20, 1935) the patient has been free from pain. She is now cooperative and grateful and has been in excellent general health. There are no subjective complaints and there has been no difficulty in swallowing.

Touch and pain sensation are absent over the posterior third of the tongue, the posterior half of the soft palate, the tonsils and fauces and the pharynx up into the nasopharynx and down to the epiglottis, and taste is gone over the posterior third of the tongue. The eustachian tube was catheterized on each side. On the right it is tender and painful, while on the left it is entirely insensitive. When the right tube is inflated, the patient complains of considerable discomfort,

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1. (*a*) Poth, E. J.: A Simplified Technique for Quantitative Collection of Salivary Secretions in Man, Proc. Soc. Exper. Biol. & Med. **30**:977 (April) 1933. (*b*) Reichert, F. L.: Neuralgias of the Glossopharyngeal Nerve, Arch. Neurol. & Psychiat. **32**:1030 (Nov.) 1934.

while on the left side she is aware only of a "click." When the external meatus or tympanic membrane on the right side is touched with cotton, there is a persistent cough, whereas on the side on which the operation was performed no cough reflex can be obtained.

As before the operation, there is a slight deviation of the uvula to the right, but the soft palate is symmetrical at rest and on movement.

The secretion of the salivary glands has been measured at intervals since operation, and the results are recorded in the table. The secretion from the parotid gland on the side of section of the glossopharyngeal nerve has been markedly decreased following operation. There has been no significant difference in the secretion of the submaxillary and sublingual glands on the two sides.

Data on the Secretion of the Salivary Glands Since Operation *

Time	Parotid Gland		Submaxillary and Sublingual Glands	
	Right	Left	Right	Left
Before operation	0.655	0.565	.....	.....
1 week after operation	1.250	0.300	.....	.....
10 weeks after operation	3.460	0.090	0.860	1.005
4 months after operation	1.635	0.265	0.645	0.550

* All values for secretion are for simultaneous periods of three minutes. The measurements are given in grams.

COMMENT

Only forty-three cases of glossopharyngeal neuralgia have been reported.[1b] The pain in most cases has originated in the pharyngeal, tonsillar or lingual branch of the nerve, and this has led to the almost axiomatic statements that glossopharyngeal neuralgia is characterized by a trigger zone in the pharynx, tonsillar fossa or posterior third of the tongue and that cocainization of these areas will relieve the pain. The fourth and last sensory branch of the ninth nerve is the tympanic branch, or Jacobson's nerve. Neuralgia limited to this branch is rare, reports of only four cases [2] having been culled from the literature. Reichert [2d] made the first evaluation of the condition as neuralgia of the tympanic plexus.

The tympanic branch supplies the eustachian tube and the middle ear, an area not readily tested for a trigger zone or anesthetized by cocaine to determine the effect on the pain. In the case here reported direct stimulation of the sensory area supplied by the tympanic branch was not carried out, nor was the area anesthetized. Nevertheless, the fact that any maneuver which increased the intrapharyngeal pressure caused a paroxysm of pain suggests that the trigger zone was in the eustachian tube or middle ear. It is suggested that in patients with

2. (*a*) Doyle, J. B.: Glossopharyngeal Neuralgia, Arch. Neurol. & Psychiat. **9**:34 (Jan.) 1923. (*b*) Adson, A. W.: The Surgical Treatment of Glossopharyngeal Neuralgia, ibid. **12**:487 (Nov.) 1924. (*c*) Keith, W. S.: Glossopharyngeal Neuralgia, Brain **55**:357, 1932. (*d*) Reichert, F. L.: Tympanic Plexus Neuralgia (True Tic Douloureux of the Ear or So-Called Geniculate Ganglion Neuralgia): Cure Effected by Intracranial Section of the Glossopharyngeal Nerve, J. A. M. A. **100**:1744 (June 3) 1933.

paroxysmal pain in the distribution of the glossopharyngeal nerve, if anesthetization of the area supplied by the pharyngeal, tonsillar or lingual branch of the nerve does not relieve the pain, cocainization of the eustachian tube and middle ear should be carried out. Failure to do this in the case reported here led to questioning the diagnosis of glossopharyngeal neuralgia, and the patient suffered unnecessarily for three years.

In neuralgia of the tympanic nerve the pain is described as beginning in the ear, usually deep and piercing, at a point just posterior to the angle and ramus of the mandible deep in the neck, neither on the surface of the skin nor on the surface of the pharynx or fauces. The latter location must represent the eustachian tube. It should be possible to demonstrate a trigger zone by catheterization of the eustachian tube. Stimulation of the external auditory meatus or the external canal did not bring on an attack. Unfortunately the drum itself was not stimulated before operation. It is possible, in retrospect, that stimulation of the drum might have set up a paroxysm.

The abolition of the cough reflex following stimulation of the external auditory meatus or tympanic membrane when the glossopharyngeal nerve has been sectioned shows that the reflex takes place by a referred sensation over glossopharyngeal fibers, and this supports the conclusion of Hunt.[3] From the findings in cases of herpes zoster oticus he concluded that the glossopharyngeal nerve supplied these parts, even though no sensory loss was demonstrable after section of the nerve.

The findings in my case on the diminution of parotid secretion following intracranial section of the glossopharyngeal nerve confirm those of Reichert and Poth.[4] The secretion of the submaxillary and sublingual glands was essentially the same on the two sides after operation. The limit of error in the measurement of the secretion of the sublingual glands is much greater than in the case of the submaxillary glands, owing to the close proximity of the ducts on the two sides.

The area of sensory loss following section of the glossopharyngeal nerve includes the pharynx on the same side from the level of the orifice of the eustachian tube, or higher, down to the epiglottis, the tonsils and fauces, the posterior half of the soft palate and the posterior third of the tongue. Taste is lost over the posterior third of the tongue. There is anesthesia of the eustachian tube, as shown by catheterization and inflation.

The glossopharyngeal nerve has one motor branch which is said to supply the stylopharyngeus muscle and also the palatopharyngeus, palatoglossus and superior constrictor muscles.[5] Tarlov's [6] macroscopic and histologic studies settle the question as to the presence of a motor com-

3. Hunt, Ramsey: The Symptom Complex of the Acute Posterior Poliomyelitides of the Geniculate, Auditory, Glossopharyngeal and Pneumogastric Ganglia, Arch. Int. Med. **5**:630 (June) 1910.

4. Reichert, F. L., and Poth, E. J.: Pathways for the Secretory Fibers of the Salivary Glands in Man, Proc. Soc. Exper. Biol. & Med. **30**:973 (April) 1933.

5. Stookey, Byron: Glossopharyngeal Neuralgia, Arch. Neurol. & Psychiat. **20**:702 (Oct.) 1928.

6. Tarlov: To be published.

ponent in the ninth nerve. He pointed out that it might be possible to preserve the motor root since it is usually distinct from the large sensory root. The secretory fibers are probably carried in the motor root, and it would be of interest physiologically to preserve it.

Intracranial section of the glossopharyngeal nerve is the treatment of choice for neuralgia of the tympanic branch of the nerve. Extracranial section, recommended by some neurosurgeons, fails to sever the tympanic branch, which arises from the petrosal ganglion and passes through a foramen in the ridge of bone between the carotid canal and the jugular fossa. Avulsion of the nerve is a hazardous procedure.

SUMMARY

A case of paroxysmal neuralgia of the tympanic branch of the glossopharyngeal nerve is reported. The paroxysms of pain were sudden and short and referred to a region deep in the neck and ear rather than to the surface of the neck or pharynx. The trigger zone was probably located in the eustachian tube, for stimulation of the mucous membrane supplied by the pharyngeal, tonsillar and lingual branches of the ninth nerve did not cause the pain and cocainization of this mucous membrane did not influence it. Intracranial section of the glossopharyngeal nerve was followed by complete relief from pain without uncomfortable sequelae.

Observations of interest as the result of this procedure are: marked diminution of parotid secretion; no detectable motor paralysis; loss of taste over the posterior third of the tongue; loss of sensation of pain and light touch over the posterior third of the tongue, the fauces, the tonsils and the pharyngeal wall from the larynx to the eustachian tube, and abolition of reflex coughing from stimulation of the external auditory meatus.

Glossopharyngeal neuralgia may involve all, or be restricted to any, of the four sensory branches of the nerve, and neuralgia of the tympanic branch merits separate consideration only because of diagnostic differences from the others.

Dr. William Cone made many helpful suggestions and gave me permission to report this case.

ABSTRACT OF DISCUSSION

DR. FRANCIS C. GRANT, Philadelphia: Glossopharyngeal neuralgia is much rarer than trigeminal neuralgia. It has a great many of the same features. The pain is paroxysmal. It is a particularly severe, stabbing, darting pain. The differential diagnosis between the two conditions depends entirely on the position of the pain. This point has been well brought out by this paper.

Patients with trigeminal neuralgia state that if they can once get food past the lips and the tip of the tongue swallowing is easy. The two patients with glossopharyngeal neuralgia whom I have observed could take food into the mouth, but swallowing was excruciatingly painful.

What interested me particularly in the case reported by Dr. Erickson was that physicians have been studying the question of pain in cases of cancer of the mouth or of the tonsillar pillar. Not infrequently a patient with cancer in these areas complains of pain deep in the ear. They dig into the external auditory canal in an attempt to relieve the pain. So far any attempts to relieve it have been entirely

unsuccessful. That may be because section of the glossopharyngeal nerve usually was attempted extracranially and not intracranially.

I feel that Dr. Erickson's finding of complete anesthesia of the eustachian tube following operation suggests that the eustachian tube and the area around it may be supplied by the glossopharyngeal nerve and that the deep-seated malignant condition in that region causing pain in the ear can be relieved by intracranial section of the glossopharyngeal nerve.

Dr. Erickson wanted to emphasize that intracranial section is a relatively simple procedure. The glossopharyngeal nerve lies fairly near to the surface. It is a definite entity, and its section is not difficult.

Clinical and Pathologic Notes

INVOLUTIONAL MELANCHOLIA

Probable Etiology and Treatment

AUGUST A. WERNER, M.D., AND LOUIS H. KOHLER, M.D., ST. LOUIS, AND C. C. AULT, M.D., AND EMMETT F. HOCTOR, M.D., FARMINGTON, MO.

Several months ago a preliminary report [1] was made on the treatment of patients with involutional melancholia by the intramuscular administration of theelin.[2] The theory on which this treatment was based was given in the original article and consists briefly of the idea that "so-called involutional melancholia is only an extreme manifestation of the symptomatology of the menopause." Great numbers of women complain during the menopause of depression, crying and decreased memory and ability for mental concentration, accompanied with mild degrees of psychosis. When these symptoms in particular (there are others at the menopause) become exaggerated, the diagnosis of involutional melancholia is made.

MENOPAUSE

The term menopause, literally meaning cessation of menstrual flow, is commonly used to designate that critical period in a woman's life more correctly spoken of as the climacteric. Menstrual pause may occur at any time during the menacme from various causes. The menopause is more than a pause or cessation of menstrual flow. This is only one of the phenomena which occur at that time. It is the one sign that is objective and therefore attracts most attention.

The pathogenic mechanism of menopausal symptomatology is not limited to insufficiency of the ovaries but is the result of a complex endocrine crisis, which varies in different persons. In this crisis the predominating feature is gonadal insufficiency (ovarian follicular hormone), but other glandular disturbances occur subsequently and form an essential part of the complex. Because of the major importance of the gonads in the endocrine system during active sexual life, insufficiency or cessation of function frequently causes imbalance in other

From the Department of Medicine, St. Louis University School of Medicine.

This experiment was conducted at the City Sanitarium, St. Louis, and at the Missouri State Hospital No. 4, Farmington, Mo.

1. Werner, A. A.; Johns, G. A.; Hoctor, E. F.; Ault, C. C.; Kohler, L. H., and Weis, M. W.: Involutional Melancholia: Probable Etiology and Treatment, J. A. M. A. **103**:13 (July 7) 1934.

2. Parke, Davis & Co. supplied the theelin used in this work.

interrelated glands, such as the anterior lobe of the pituitary, the thyroid and the adrenals (the medulla and in some instances the cortex).

With the disturbance of function in the ovaries and other interrelated glands there is a secondary disturbance of the delicate equilibrium existing between the two divisions of the autonomic nervous system, with the production of symptoms and signs which are reflected in the nervous, circulatory and somatic systems. In other words, most of the symptoms occurring at this time are the result of instability of the autonomic nervous system secondary to endocrine imbalance.

DURATION OF THE MENOPAUSE

It is important that the duration of the menopause be stressed. The menopause varies in duration with each person just as the menacme does. Some women enter the menopause at 38 and others at 50 years of age. Frequently a woman menstruates until the age of 56. In some women the symptoms of the menopausal period may be not noticeable or fleeting; in others, the syndrome may last from three months to five or six years or even more. Some women claim to have had no appreciable disturbance at the time of cessation of menstruation and perhaps five or ten years later, at ages from 50 to 60, experience the typical menopausal syndrome, which responds to treatment.

If a woman the duration of whose menopause (time for endocrine equilibrium to occur) is only from three to six months should experience involutional melancholia and be treated properly with theelin for six months, with recovery, one can expect that she will not have a relapse. However, if a woman whose menopausal disturbance is going to be of from four to five years' duration should acquire involutional melancholia, she will need prolonged and intermittent treatment. She should be studied, and if there is evidence of recurrence of the condition medication should be instituted at once, before a severe relapse occurs. Since theelin has been put in oil in high concentration (300 rat units, Doisy, per cubic centimeter), which causes slower absorption and more prolonged effect, it might be better to give an injection of 1 ampule weekly for an extended time after the preliminary treatment to prevent relapse in patients whose syndrome will be of long duration.

TREATMENT

The dosage of theelin administered to the patients in the present study was arbitrarily set at 1 cc. of aqueous solution (50 rat units per cubic centimeter) daily for six months. We thought that six months is sufficient time for a fair trial and that if no results are obtained at the end of that time theelin will not benefit the patient. It must not be understood that all patients who will recover will do so within six months. If they improve they must be treated indefinitely until well. We have had the experience in some later cases not included in this report that the administration of 1 cc. of theelin in oil (300 rat units per cubic centimeter), given intramuscularly twice weekly, is just as effective as our previous daily dose of 1 cc. of aqueous solution (50 rat units).

RESULTS

Report for First Six Months.—In this experiment we treated forty patients with involutional melancholia. Twenty were given 1 cc. of theelin in aqueous

TABLE 1.—*Results in Treated Patients and Controls at the End of Six Months**

Treated Patients	Age	Duration of Psychosis	Improvement	Control Patients	Age	Duration of Psychosis	Improvement
1. M. B.	56	6 yr.	Slight	22. E. B.	46	5 yr. 4 mo.	None
2. D. S.	56	5 yr.	Moderate	23. M. W.	58	9 yr. 4 mo.	None
3. L. S.	50	5 yr.	None; cerebral sclerosis	24. M. S.	55	6 yr. 4 mo.	None
				25. J. S.	48	3 yr. 4 mo.	Slight
4. M. W.	50	2 yr. 6 mo.	Marked	26. E. D.	58	3 yr. 4 mo.	Moderate
5. M. K.	57	4 yr.	Moderate	27. F. M.	48	2 yr. 9 mo.	None
6. L. Z.	55	7 yr.	Marked	28. E. A.	53	3 yr. 9 mo.	None
7. B. F.	52	3 yr. 6 mo.	Marked	29. E. C.	58	4 yr.	None
8. C. F.	50	1 yr. 4 mo.	None; cerebral sclerosis	30. H. S.	53	8 yr. 4 mo.	None
				31. C. G.	48	1 yr. 4 mo.	None
9. E. M.	49	8 yr.	Moderate	32. A. S.	56	11 yr. 4 mo.	None
10. M. K.	58	6 mo.	Marked	33. A. R.	45	1 yr. 3 mo.	None
11. A. Z.	57	2 yr. 6 mo.	Marked	34. L. B.	54	4 yr. 3 mo.	None
12. L. K.	47	6 mo.	Marked	35. M. K.	47	11 mo.	None
13. A. S.	50	8 mo.	Marked	36. C. S.	46	2 yr. 10 mo.	None
14. F. J.	47	1 yr. 11 mo.	Marked	37. H. F.	48	4 mo.	Moderate
15. A. M.	43	8 mo.	Marked	38. M. F.	54	4 mo.	None
16. D. B.	46	4 mo.	Slight	39. L. H.	45	5 yr. 3 mo.	None
17. A. S.	52	2 yr. 7 mo.	Marked	40. E. S.	55	6 mo.	None
18. M. D.	44	1 mo.	Marked				
19. S. E.	52	3 mo.	Slight				
20. R. T.	34	11 mo.	Marked				
21. F. R.	45	8 mo.	Marked				
Average	49.7	2.54 yr.		Average	51	3.93 yr.	

* Treated patients were given daily injections of 1 cc. of theelin intramuscularly, and controls, daily injections of 1 cc. of physiologic solution of sodium chloride intramuscularly. In cases 1 to 21 there was marked improvement in 13, or 61.9 per cent; moderate in 3, or 14.2 per cent; slight in 3, or 14.2 per cent; and none in 2, or 9.5 per cent. In cases 22 to 40 there was marked improvement in none; moderate in 2, or 10.5 per cent; slight in 1, or 5.2 per cent, and none in 16, or 84.2 per cent.

TABLE 2.—*Condition of Nineteen Control Patients After Receiving Injections of Physiologic Solution of Sodium Chloride for Six Months Followed by 1 Cc. of Theelin for Six Months**

Control Patients	Age	Improvement after the Administration of Physiologic Solution of Sodium Chloride	Improvement after the Administration of Theelin
22. E. B.	46	None	Moderate
23. M. W.	58	None	Marked
24. M. S.	55	None	Marked
25. J. S.	48	Slight	Marked
26. E. D.	58	Moderate	Marked
27. F. H.	48	None	Marked
28. E. A.	53	None	Moderate
29. E. C.	58	None	Cerebral sclerosis
30. H. S.	53	None	Schizophrenia
31. C. G.	48	None	Marked
32. A. S.	56	None	Marked
33. A. R.	45	None	Schizophrenia
34. L. B.	54	None	Marked
35. M. K.	47	None	Schizophrenia
36. C. S.	46	None	Schizophrenia
37. H. F.	48	None	Marked
38. M. F.	54	None	No theelin
39. L. H.	45	None	Moderate
40. E. S.	55	None	Moderate

* With daily injections of 1 cc. of physiologic solution of sodium chloride there was no improvement in 16 patients, or 84.2 per cent; moderate in 2, or 10.5 per cent, and slight in 1, or 5.2 per cent. With daily injections of 1 cc. of theelin intramuscularly there was marked improvement in 8, or 44.4 per cent, and moderate in 5, or 27.7 per cent. Involutional melancholia complicated by other forms of mental disease was present in 5, or 27.7 per cent.

solution (50 rat units) intramuscularly daily for six months, and twenty controls were given 1 cc. of physiologic solution of sodium chloride intramuscularly daily for the same period of time. Table 1 shows the beneficial results obtained by the use of theelin and the failure to secure results with physiologic solution of sodium chloride.

Control Patients.—After the control patients had failed to benefit by injections of physiologic solution of sodium chloride, they were given 1 cc. of theelin (50 rat units, Doisy) intramuscularly daily for six months, with the results shown in table 2.

INVOLUTIONAL MELANCHOLIA COMPLICATED BY OTHER TYPES OF MENTAL DISEASE

Involutional melancholia may obscure the presence of other types of mental disease. There are patients who, perhaps for years, have been verging on dementia praecox or some other form of mental disorder and who at the menopause have involutional melancholia. The stress of the nervous and mental shock at this time brings the dormant potentiality to the surface and the patient may then have two mental diseases, involutional melancholia masking the secondary disorder. Occasionally a patient shows evidence of cerebral sclerosis with mental deterioration. It is our experience that the symptoms of involutional melancholia are relieved in these patients, and then the other disorder stands out prominently.

Tables 1 and 2 show that in cases 3, 8 and 29, in which the symptoms were those of involutional melancholia which improved to some degree under therapy with theelin, the patients now present the symptoms of cerebral sclerosis with deterioration.

We have found that if a patient who has had a previous mental disturbance suffers from involutional melancholia the prognosis is not so favorable.

In case 3 there was evidence of mental retardation at the age of 5. The patient was maladjusted during preadolescence, being seclusive, stubborn and resistive to supervision. With adolescence she became more seclusive, evidenced phobias about cleanliness and the preparation of food and had peculiar mannerisms. The patient in case 33 had been confined in two institutions previous to coming under our supervision. The patient in case 35 had an aunt and an uncle who were mentally ill. The patient in case 36 had a sister who had a mental disease and a cousin who was feebleminded.

Table 2 shows that in cases 30, 33, 35 and 36 the patients now present evidence of the various types of schizophrenia which had been masked previously by the symptoms of involutional melancholia. Under therapy with theelin the involutional symptoms disappeared sufficiently to make the diagnosis of schizophrenia definite.

COMMENT

The average age of the patients was 50.3 years (minimum 34, maximum 58). The average age at onset of symptoms was 47 years. The average duration of symptoms before theelin was administered was three and twenty-eight hundredths years (minimum one month, maximum eleven years and four months). It is reasonable to believe that cases in which there has been mental imbalance for as long as

eleven years will show deterioration and will not offer as good a prognosis as if treatment had been instituted within the first six months after the onset. Table 3 summarizes the completed experiment. After the administration of 1 cc. of theelin (50 rat units, Doisy) intramuscularly daily to thirty-nine patients with involutional melancholia, twenty-one, or 53.84 per cent, showed marked improvement, which means that they had recovered completely or sufficiently to lead normal social lives. Eight patients, or 20.51 per cent, showed moderate improvement. It is our experience that most of these patients will continue to improve under treatment to recovery. Three patients, or 7.2 per cent, show only slight improvement; they may improve more with continued treatment, but the prognosis for the present is guarded.

Seven of the patients data for whom are included in the figures in table 3 had some other form of mental disease complicating the involutional melancholia. If the results in these seven patients are eliminated,

TABLE 3.—*Summary of Data on the Treatment of Patients with Involutional Melancholia and Controls with Theelin for a Period of Six Months* *

	Patients	Improvement			
		Marked	Moderate	Slight	None
Results after administration of theelin to patients for 6 months	21	13 61.9%	3 14.2%	3 14.2%	2† 9.5%
Results after administration of physiologic solution of sodium chloride to controls for 6 months	19	None	2 10.5%	1 5.2%	16 84.2%
Results after administration of theelin to controls for 6 months	18	8 44.4%	5 27.7%	None	5† 27.7%
Final results after administration of theelin to all patients for 6 months	39	21 +53.84%	8 +20.51%	3 −7.20%	7† −17.9%

* The final results, if 7 patients with involutional melancholia complicated by other forms of mental disease are eliminated, show marked improvement in 21, or 65.66 per cent; moderate in 8, or 25 per cent, and slight in 3, or 9.37 per cent.

† Complicated by other forms of mental disease.

a much brighter picture is presented: marked improvement, 65.66 per cent; moderate improvement, 25 per cent. A number of the moderately improved patients will later show marked improvement and will increase the percentage of that number.

CONCLUSIONS

1. Theelin is curative in cases of uncomplicated involutional melancholia.

2. Theelin accelerates recovery and shortens the period of mental illness or involutional melancholia.

3. The prognosis is favorably influenced by early diagnosis and treatment.

4. A history of previous mental disorder in the patient suggests a guarded prognosis.

5. The administration of theelin may be used as a therapeutic diagnostic test to differentiate between involutional melancholia and other types of mental disease occurring at the menopause.

SPECIAL ARTICLES

DISCOVERY OF THE AUTONOMIC NERVOUS SYSTEM

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No field of biologic science is at present attracting closer attention than the autonomic nervous system. Its problems are being assailed from all angles, morphologic, physiologic, chemical and clinical, and each line of attack is yielding new knowledge. Peripherally, the intricate pattern of neurons is becoming linked with humoral physiology; centrally, higher mechanisms for control are being discovered which appear to coordinate the autonomic and somatic functions into a still more harmonious whole. Bichat's original concept of the complete independence of the "organic" nervous system is being abandoned, and the significance of Bernard's broad conception of the *milieu intérieur* has at last come into its own.

New ideas springing up in the full tide of present-day knowledge leave behind a feeling of instability and uncertainty, and yet despite many doubts certain fundamental concepts have emerged from the mass of evidence gathered in the past. The growth of such ideas is not merely of historical interest. The light of the past, it has been said, shines through the present, and if the future developments in this field are to be correctly predicted a study of these ideas must inevitably illuminate the present-day outlook.

It is unfortunate that no adequate historical survey of the discovery of the autonomic nervous system exists. Apart from brief introductory comments in recent textbooks, Langley's excellent and comprehensive review of the progress in this branch during the eighteenth century remains the sole contribution. From almost the dawn of medicine, however, medical thought has dwelt on the possible implication of the visceral nervous system in disease, and many, indeed, have been the conceptual streams flowing through the centuries, precipitated suddenly in cascades of experimental investigation. It is impossible to do full justice to all the views that have contributed to the final picture, and the present outline is offered *pour préciser les idées.*

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With Greek medical thought the story of the autonomic nervous system inevitably begins.

EARLY CONCEPTS

Dawn appeared over the central nervous system with the illustrious names of Erasistratus and Herophilus, two Alexandrian anatomists in the fourth century B. C., from whose independent investigations the first clear descriptions of the brain and spinal cord were drawn. Herophilus has been immortalized by the torcular which bears his name, but it is not generally known that he was the first to differentiate the cerebrum and the cerebellum, to describe the meninges and fourth ventricle and to enumerate the cranial nerves and deduce their motor and sensory functions. Between the time of these early fathers of neurologic anatomy and that of Galen, no record exists of investigations on the central nervous system.

Galen, born at Pergamon, Mysia, in 130 A. D., contributed to the great revival of Greek culture under the Roman Empire. The revival, which was characterized by skepticism of authority and desire to investigate all traditional statement, led to two fundamental developments in the progress of neurology: the introduction of the experimental method and the correlation of structure and function. It resulted in Galen's work on spinal cord section, his experimental proof of the function of the recurrent laryngeal nerve and his demonstration that ligature of a peripheral nerve was followed by loss of both motor power and sensation in the area of distribution.

Galen's[1] hypothesis of the generation of animal spirits by the brain offered the first widely accepted interpretation of the phenomenon of "sympathy" or "consent" between different parts of the body, a view which pervaded physiologic thought until the beginning of the last century. Rejecting Aristotle's teaching that the brain served to cool the blood, Galen attributed to it the office of generating "animal" spirits from the "vital" spirits which were believed to flow in the blood. Although such a conception met with much opposition and it was argued that "a most subtil Spirit cannot be made in a cold Brain and full of mucous Filth; for cold stupifies the Spirits and hinders their Actions," nevertheless the idea gradually gained acceptance, and questions, which remained preeminent until the start of the eighteenth century, arose concerning the exact place of origin of the animal spirits. It is unnecessary here to discuss these purely speculative views except to quote the remarkably prophetic sentence of de Diemerbroeck, written in 1694: "Many others believe, that the Animal Spirits are elaborated

1. Brief mention of Galen's views on the sympathetic and vagus nerves occurs in "De usu partium."

in the Choroidal Fold, and that the Vital Blood in its passage through the Fold is altered into these Spirits by a singular propriety of the Brain."

The animal spirits, so generated, were supposed, according to the ancients, to flow under the force of wavelike motions of the brain along the peripheral nerves, which were considered to be hollow tubular structures. By some it was thought that the spirits moved both to and from the brain, thus giving rise to sensation and motion, respectively, by others, that a rapid and sudden flow of spirits along the nerves caused the distention of the muscle in contraction and that slower and more constant passage of spirits accounted for sensation. Wherever peripheral nerves joined, communications between the tubes were thought to exist, thus allowing the animal spirits to flow with ease from one part of the body to another and thereby accounting for the "sympathy" between various parts of the body.

Galen enumerated seven pairs of cranial nerves, the olfactory, trochlear and abducens nerves being omitted from his classification. Of the "sixth pair" he described three main branches, the superior and recurrent laryngeal nerves and a costal branch, running along the roots of the ribs, receiving fibers from the thoracic and lumbar portions of the spinal cord and being distributed to the viscera. The viscera thereby received from the brain an "exquisite" sensitivity and from the spinal cord their motor power. This is the earliest description of the vago-sympathetic trunk and of the rami communicantes as they are known today.

Along the course of the "sixth pair" Galen observed three swellings or ganglia on each side, the first situated in the neck, just above the larynx, the second as the nerve enters the thorax and the third at the entrance of the nerve into the abdomen. There can be little doubt from Galen's description that he referred to the superior cervical, the inferior cervical and the semilunar ganglion, respectively, although it seems likely that he described the superior cervical ganglion and the ganglion of the vagus trunk as one, a mistake followed by many later anatomists. The function of the ganglia was to serve as buttresses to strengthen the nerves as they receded from their origin. To Galen, therefore, and not to Fallopio, as is generally supposed, should go the credit for the first account of the ganglia of the sympathetic nervous system. That Fallopio was the discoverer of the ganglia is clearly a mistake of Lancisi, handed down to posterity by Haller.

The description of the "sixth pair" of cranial nerves, given by Galen and religiously followed by all anatomists until and including Vesalius (fig. 1), grouped the vagus nerve and the ganglionated trunk of the sympathetic system as one, both anatomically and physiologically.

Etienne (1545) and later Eustachio (1552) first distinguished the two nerves anatomically. The notes of Eustachio were published without illustrations in Venice in 1563, eighteen years after the appearance of Etienne's work. The drawings of the Eustachian dissections [2] were left on his death to his friend and relative Pini. In 1714 thirty-eight copperplates were discovered in the care of the Rossi family (descendants of Pini) and published by Lancisi. The descriptive notes accom-

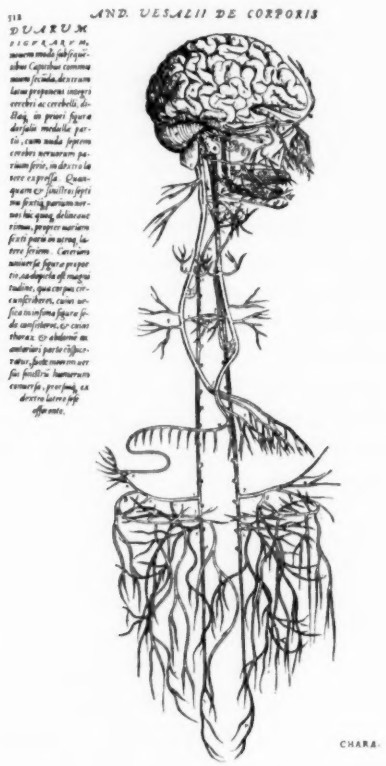

Fig. 1.—The earliest drawing of the "sixth pair" of cranial nerves (according to Galen's classification). The vagus nerve and the cervical portion of the sympathetic trunk are represented as one trunk. The thoracic and abdominal portions of the sympathetic chain and the rami communicantes are clearly shown (from Vesalius, A.: Suorum de humani corporis fabrica, ed. 2, 1555).

panying the plates were supposedly lost, but it is conceivable that they were included in the "Opuscula anatomica" of Eustachio, published during his lifetime. It is clear that both Etienne and Eustachio recognized the double nature of the nerve trunk in the neck. Eustachio pic-

2. Copper plates were made in 1552.

tured the sympathetic component as arising within the cranium from the abducens nerve, thus giving to the sympathetic system a cerebral origin (fig. 2), a fallacy not corrected until 1727, by the work of du Petit. The connections of the rami communicantes were, however, accurately portrayed by Eustachio, and Haller gave him the additional credit for the first description of the splanchnic nerves, though this distinction seems more fairly to belong to Galen.

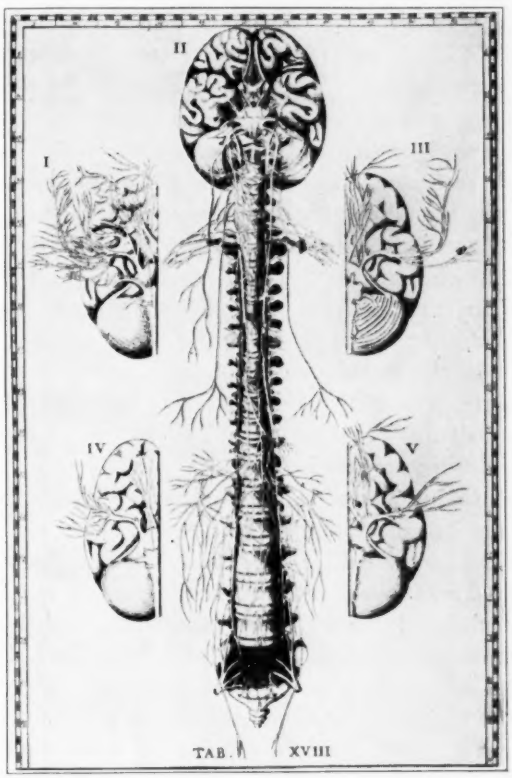

Fig. 2.—The supposed cerebral origin of the cervical portion of the sympathetic trunk from the abducens nerve. The separate course in the neck of the vagus nerve and the sympathetic trunk had by this time been recognized. The superior cervical ganglion and some of the lower sympathetic ganglia are shown (from Eustachio, B.: Tabulae anatomicae, 1714 [Copperplates made in 1552]).

Willis (1621-1675) stood on the threshold of a new era in neurology. His physiologic writings were largely expressions of hellenic concepts and were often purely speculative. He was, however, a clinician of the hippocratic tradition of close observation, and his complete and accurate anatomic descriptions of the nervous system have formed the basis of present-day nomenclature. Willis' contribution to

neurology has been eclipsed by the fame he won through the discovery of the arterial circle at the base of the brain, illustrated by his pupil Sir Christopher Wren, but Willis' "Cerebri anatome" represents an important milestone along the road to knowledge of the autonomic nervous system.

From the standpoint of anatomy, Willis introduced the basis of the modern nomenclature of the cranial nerves, and to him is attributed the discovery of the spinal accessory nerve. The vagus or "wandering" nerves (from this time referred to as the "eighth pair") were accurately described, and Willis noted the branch given off to the arch of the aorta, "so it may react to changes in the pulse" (surely the earliest reference to the depressor nerve). The apparent union in lower animals of the cervical portion of the sympathetic trunk and the vagus nerve and their separate course in man were recognized and illustrated (fig. 3). To the ganglionic chain Willis gave the name "intercostal" nerve, "because passing near the roots of the ribs it receives in every interspace a branch from the spinal marrow," and this designation persisted until the time of Winslow. Willis, however, perpetuated the error of Eustachio in ascribing an intracranial origin to the "intercostal" nerve. As the drawings of Eustachio were not published until 1714, almost fifty years after the appearance of Willis' "Cerebri anatome," it is evident that the observation of Eustachio must have become widely known during his lifetime.

In addition to his anatomic contributions, Willis was one of the first to introduce into scientific thought the conception of "involuntary" as distinct from "volitional" movement. The explanation, however, which he offered was based entirely on the galenic teaching. To the cerebellum he assigned the office of generating animal spirits which engendered involuntary action, such as the heart beat, breathing and gastro-intestinal movements, and to the cerebrum, the production of spirits for voluntary acts. This view rested on certain evidence which, though merely suggestive, undoubtedly carried at the time considerable weight. Willis argued from four standpoints. From the anatomic approach he observed that the nerves from the cerebellum were distributed to the thoracic and abdominal viscera and to the face and eyes, structures which were known to participate in involuntary action. It is important to understand that Willis believed that the pons and the inferior cerebellar peduncles were part of the cerebellum and that thus the trigeminal, abducens, facial, auditory and vagus nerves, in addition to the "intercostal" nerve, at this time considered to possess an intracranial origin from the abducens nerve, all arose from the cerebellum. Morphologically, Willis observed that the cerebellum in lower forms did not vary in size and development as did the cerebrum. Involuntary motion was equally present in all animals, whereas skilled volitional acts were manifest proportionally to the degree of development of the

cerebrum. A third line of evidence was adduced from the experimental method, for injury of the cerebellum in animals, it was found, was followed almost invariably by abolition of involuntary action. In particular, the instantaneous cessation of the heart beat and respiration had been noted. Lastly, on the basis of clinical studies of cerebellar lesions Willis pointed out that sudden jerking of the head backward frequently resulted in loss of consciousness, with irregularities in the heart beat and respiration.

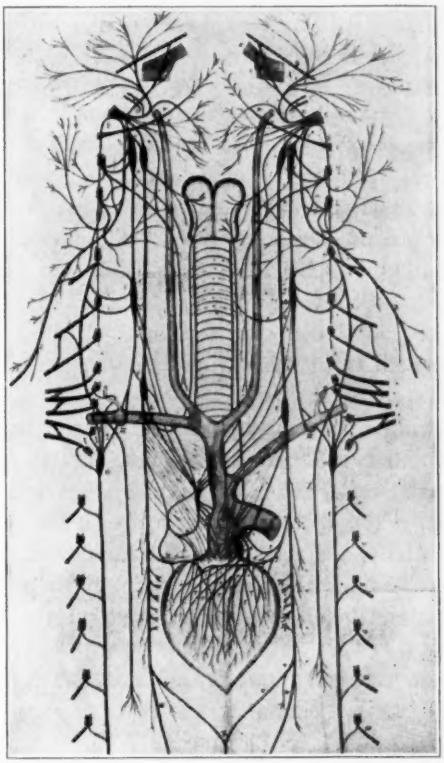

Fig. 3.—Schematic representation of the vagus nerve and the cervical portion of the sympathetic trunk in man. Their apparent union in lower animals is illustrated in a later figure. The intracranial origin of the sympathetic trunk is again depicted (from Willis, T.: Cerebri anatome, 1644).

In a further development of this hypothesis of cerebellar function, Willis enlarged the galenic conception of "sympathy." Such phenomena were explicable, according to Willis, on the basis of a flow of "involuntary" animal spirits through the communications of the nerves, more specifically the vagus and the "intercostal" nerve, or, in the cases in which no nerve connections existed between the parts, via a longer pathway through the cerebellum. The nerve channels were considered

to convey the spirits both to and from the cerebellum, a restatement of an earlier view of afferent and efferent pathways, but the idea of separate nerves for these functions had not yet been considered. Willis added, however, that ascending impressions from the thoracic and abdominal viscera, if strong, could pass through the cerebellum into the cerebrum and so become "conscious." Similarly, volition could on suitable occasions be exerted from the cerebrum through the cerebellum on the visceral structures, thus explaining the semivoluntary control of the will over certain involuntary acts, such as breathing. There is unquestionably a modern ring to such a view of higher and lower levels in the central nervous system.

Willis expressed the belief that the rami communicantes of the "intercostal" nerve served to strengthen the nerve on the long course from its origin, to bring together the "involuntary" spirits from the cerebellum and the "voluntary" spirits from the brain and spinal cord and, lastly, to act as excretory channels for superfluous spirits in the central nervous system. The ganglia or "infoldings," as Willis called them, acted as storehouses for the spirits. Though purely speculative, such statements do not in any way detract from the accuracy and importance of his anatomic contributions. Willis' account of the branches and connections of the various ganglia remains the first comprehensive description of its kind.

Thus, by the end of the seventeenth century the "intercostal" (sympathetic) and "wandering" (vagus) nerves, though clearly separated anatomically, remained physiologically one system, possessing a double function. Primarily, the system served to originate involuntary movements, and secondarily, on account of its numerous intercommunications, it was looked on as the modus operandi by which "sympathy" could be brought about between different parts of the body.

REINTRODUCTION OF EXPERIMENTAL METHOD: LOWER, WHYTT AND HALLER

With the reintroduction of the experimental method by Galileo and Harvey there was ushered in a new era in the history of the autonomic nervous system. The growth of two ideas in particular can be discerned in the progress of thought during this second period.

First, the importance of the vagus nerve in the innervation of the heart gradually became recognized. Willis had found that bilateral section of the vagus nerve in a dog was followed by unconsciousness and "great trembling" of the heart. The animal survived many days, and Willis offered as an explanation of this phenomenon that the heart received sufficient animal spirits from the "intercostal" and recurrent laryngeal nerves. The problem was taken up by one of his pupils,

Lower, who introduced the technic of experimental perfusion of organs and in 1669 published the earliest observations on the heart beat after stimulation (by ligature) and section of the vagus nerve. The findings were confirmed and amplified by the work of Ens in 1745 and led finally to the establishment by the Webers in 1845 of the inhibitory action of the vagus nerve on the heart beat.

Second, the classification of "involuntary" movements by Whytt and his interpretation on a basis of local stimulation introduced an entirely new line of physiologic thought and laid a substantial foundation for the neuron doctrine and the theory of reflex action.

Whytt's publication (1751) on the involuntary motions of animals showed extraordinary powers of critical judgment and reasoning and elaborate care in presenting experimental data to support every opinion he expressed. One must realize that Whytt's background was the galenic doctrine of animal spirits and the theory of involuntary motion dependent on the cerebellum, as expounded by Willis. While he never quite rid himself of the latter interpretation, Whytt showed in his writings probably the first trend of scientific thought away from the galenic tradition. He wrote:

> The immediate cause of muscular contraction, which, from what has been said, appears evidently to be lodged in the brain and nerves, I chuse to distinguish by the terms of the *power* or *influence of the nerves;* and if, in compliance with custom, I shall at any time give it the name of *animal* or *vital* spirits, I desire it may be understood to be without any view of ascertaining its particular nature or manner of acting; it being sufficient for my purpose that the existence of such a power is granted in general, though its peculiar nature and properties be unknown.

Whytt extended greatly Willis' differentiation of animal motions into voluntary and involuntary movements, and, as it was obvious that some muscular contractions, though subject to the power of the "will," are not ordinarily directed by it, these motions were designated as "mixed." The germ of the idea of muscular tonus can also be found in Whytt's writings.

> The muscles of live animals are constantly endeavouring to shorten or contract themselves. Hence such as have antagonists are always in a state of tension . . . The natural contraction of the muscles is in a great measure to be ascribed to the influence of the nerves, which is perpetually operating upon them, though in a very gentle manner.

Whytt's explanation for "involuntary" movements was "local stimulation." Thus, in the heart the blood acted "as a gentle stimulus to those sensible nerves and membranes which line the auricles and ventricles of the heart." A further stimulus was that of the mechanical stretching of the muscular fibers—"the distension of hollow muscle has a remarkable influence towards exciting them into action." Whytt

understood the importance of the adequate stimulus (the significance of which was completely overlooked in later work on visceral sensibility), for he repeatedly pointed out that the stimulating agent for one structure may have no such effect on another.

> Although the outer surface of the heart and intestines may have no great degree of sensibility, it will not thence follow that their internal surface, where the natural stimuli exciting their motions act upon them, is not endowed with a more exquisite feeling.

The contractions of the bladder and the peristaltic movements of the alimentary canal were also explained on a basis of local stimulation, by irritation of nerves locally and by mechanical stretching of the muscular fibers by distention. The close similarity of such an interpretation and that of the present day, despite the extensive body of information that has since been added concerning the submucosal and myenteric plexuses, makes Whytt's concept all the more remarkable. Without knowledge or, indeed, any theoretical conception of a reflex nervous path, Whytt nevertheless introduced for the first time the idea of reflex action, emphasizing the effective response to an affective stimulus, dependent at least in part on the integrity of nerve connections.

His application of this principle to the motions of the pupil is noteworthy as the earliest known records of the light, accommodation and consensual reflexes. In discussing the pupillary motions Whytt writes:

> As in the shade it is remarkably large, and always the more so, the greater the darkness; while in a bright light it is contracted almost to a point; it clearly follows, that the co-arctation of this passage is owing to the action of light on the eye as a sensible organ, and its dilatation to the superior contractile power of the longitudinal fibers of the uvea, when the eye is left to itself, and not affected by any external cause. The pupil is contracted more or less in proportion to the quantity of light admitted into the eye, not on account of any immediate action of this subtile fluid on the fibers of the iris, as some have imagined, but in consequence of its affecting the tender retina with an uneasy sensation.
>
> The motions of the pupil are not only necessary to adapt the eye to different degrees of light, but also to the distinct vision of objects at different distances. Thus if a book which one can easily read at the distance of two feet, is gradually brought nearer the eye, till the letters can be no longer distinguished, the pupil will be observed to become narrower in proportion as the book approaches the eye.

Whytt noted that in the blind eye there is no response of the pupil to light but that when the sound eye is exposed to the sunlight the pupil of the blind eye immediately contracts.

> This contraction can only arise from the sympathy between the two pupils; and shews, that when the sound eye is covered, the defect of motion in the morbid one is not owing to the nerves of the uvea being any way paralytic, but merely to the want of a cause determining their influence into the orbicular muscle of the pupil.

Whytt expressed the belief that muscular contraction is dependent on the integrity of the nerves, but his analysis was often obscured by transgressions concerning the seat of the soul or "sentient principle," on which all vital (involuntary) and animal (voluntary) movements ultimately depended.

In a later work (1765) Whytt discussed in greater detail the various "sympathies." In the eighteenth century many and varied phenomena had been thrown loosely under this cloak of ignorance. The list included the vomiting and nausea associated with headache, the spread of inflammation from one eye to the other, the contraction of the pupil when light is cast into the opposite eye, the flow of saliva on the sight or smell of food, the itching of the nose in cases of parasitic infection of the intestine, "the pain between the vertebrae of the neck and the top of the shoulder" in cases of inflammation of the liver and diaphragm, the frequent micturition and pain in the tip of the penis in cases of renal calculus, the mammary changes during pregnancy and after delivery and the convulsions and lockjaw following wounds of the sole of the foot.

The prevailing opinion was that of Willis, i. e., that such "sympathies" were due to communications between the nerve tubes issuing from the cerebellum, more specifically those belonging to the "eighth pair" and to the "intercostal" nerve. Whytt argued that all "sympathy" or "consent" presupposed feeling and must therefore be dependent on nerves, which were the sole instruments of sensation. He added:

> Since every individual nerve appears to be quite distinct from every other, not only in its rise from the medullary substance of the brain or spinal marrow, but also in its progress to that part where it terminates, it follows, that the various instances of sympathy, observed between the different parts of the body, cannot be owing to any communication or anastomosis of their nerves . . . If, therefore, the various instances of sympathy cannot be accounted for from any union or anastomosis of the nerves, in their way from the brain to the several organs; and if there are many remarkable instances of consent between parts whose nerves have no connection at all; it follows that all sympathy must be referred to the brain itself and spinal marrow, the source of all the nerves.

Whytt thus introduced two new concepts, which had far-reaching application. First, he drew attention to the existence of nerve fibers as single units, in contradistinction to the older view of anastomosing channels, and thus laid the foundations for the neuron doctrine, and second, his interpretation of "sympathy" called attention to the central connections of the afferent nerves, and was an unquestionable forerunner of MacKenzie's theory of an "irritable focus" in the cord to explain the phenomenon of referred pain.

Haller has been wrongly credited by Gaskell with the discovery of the rami communicantes, but there is nothing in any of Haller's writ-

ings to indicate that he understood the real significance of these connections. His contribution to the physiology of the autonomic nervous system lies largely in his experimental endeavors to ascertain the sensibility of the viscera. In his treatise on the sensible and irritable parts of animals, published in 1760, Haller attributed sensibility to nerves, but he expressed the belief that irritability (contractility) was a function entirely of muscle, independent of nervous influence. He divided the structures of the body into distinct categories, sensible and insensible, and irritable and nonirritable parts, and thereby delayed for over a century the development of the theory of reflex action, the seeds of which had been so admirably sown by Whytt in his attempted correlation of sensory and motor functions.

By repeated experimentation with animals, however, Haller first established the insensibility of the peritoneum, pleura and pericardium to mechanical stimulation. He attributed the lack of sensation to an absence of nerve supply, and in contrast to Whytt's keen analysis, there is no indication in his writings of appreciation of the "adequate stimulus." Thus began the first experimental work on visceral sensibility.

FUNCTIONS OF GANGLIA

An important contribution to the physiology of the sympathetic nervous system had been made in 1727 by the French surgeon Pourfour du Petit. By careful dissection and then by experimental section of the vagosympathetic trunk in the neck in dogs, Petit dealt the deathblow to the proposed cerebral origin of the "intercostal" nerve. He gave the first accurate account of the Horner syndrome, distinguishing clearly between the respiratory embarrassment due to vagal section and the ocular palsy due to paralysis of the cervical portion of the sympathetic trunk. It was a century and a half, however, before the full significance of Petit's observations became realized. Although one can see in the works of subsequent writers clear recognition that the only possible pathway from the central nervous system to the sympathetic ganglia is through the rami communicantes, it was not until the time of Gaskell and Langley that such a logical inference became enunciated clearly and proved experimentally.

Winslow (1732), it is true, accepted Petit's results, but, turning to the other possible explanation, he saw in the sympathetic ganglia independent centers of nervous control, thus foreshadowing Bichat's notable concept of the complete independence of the organic nervous system. Winslow wrote:

> These ganglions differ more or less from each other in size, color and consistence; and may be looked upon as so many origins or germina dispersed through this great pair of nerves, and consequently as so many little brains.

Winslow's influence can also be traced in his suggestion of the name "great sympathetic nerve," perhaps an unfortunate term in the light of the present-day ambiguity in terminology. His reasons for such a change were obviously based on the belief that the "intercostal" nerve in its intricate ramifications was concerned primarily with the production of "sympathies" between various organs.

> These nerves, as I have said, are commonly called intercostales, though this name does not agree either with their situation, or with the extent of their course, as we shall presently see; therefore I believe the name of sympathetici majores, or maximi, will be more proper, because of their frequent communications with almost all the other principal nerves of the body.

Lancisi is of importance largely because he published the eustachian plates. His account of the functions of the ganglia appeared in 1718 and expressed the view, which he attributed to his teacher Morgagni, that the ganglia acted as muscular pumps to propel animal spirits along the nerves. Involuntary motion was believed to be due to a continuous influx of spirits, and voluntary motion, to a sudden increase in the flow, brought about by the contraction of muscle fibers within the ganglia. The treatise shows little insight into the newer developments of physiologic thought and expressed a purely hypothetic idea, without any serious attempt at experimental verification.

In 1764 an important contribution by Johnstone served to dispel any belief in the hypothesis put forward by Lancisi. Johnstone noted that the ganglia were noncontractile and apparently contained no muscular tissue. Furthermore, they were confined almost entirely to nerves distributed to parts the motions of which were totally involuntary, and Johnstone postulated that they were "the instruments, by which the motions of the heart and intestines are, from the earliest to the last periods of animal life, rendered uniformly involuntary. . . . The determinations of the will are, as it were, intercepted, and prevented from reaching certain parts of the body, by means of ganglions." In a similar manner the ganglia were considered to interrupt sensory impressions from these parts, thus accounting for the slight and vaguely localized sensibility of such visceral structures. "Confused or indeterminate sensation is proper to parts whose nerves arise from ganglions."

The ganglia on the dorsal spinal roots, Johnstone stated, affected only those fibers passing to the sympathetic trunk, leaving the remaining fibers "free for the conveyance of the commands of the will." The ganglion on the fifth cranial nerve seemed to offer greater difficulties, but observing that the fibers of this nerve were distributed to the salivary and mucous glands of the mouth and nose, Johnstone pertinently asked: "May they not be supposed to have some use in glandular secretion?"

Johnstone was one of the few who saw clearly the logical inference of Petit's experiment, for he spoke of the spinal marrow "from which the intercostal, or great sympathetic, nerves which supply the heart and intestines truly arise." Despite this, however, he leaned definitely toward Winslow's view of semi-independence of the ganglionic system and no doubt thereby aided in the propagation of this concept, at least in England.

Two further observations of Johnstone are worthy of special mention, although their significance has become evident only in the light of recent knowledge. He noted that ganglia are formed generally at the junction of several nerves and, further, that the bulk of any ganglion exceeds by far that of all the nerves and blood vessels which enter it. The cellular nature of the ganglia was not worked out until more than fifty years later, yet Johnstone gave a remarkably accurate account of their gross appearance.

> The ganglions, respecting their structure, may justly be considered as little brains, or germes, of the nerves detached from them, consisting of a mixture of cortical, and nervous medullary substance, nourished by several small blood vessels, in which, various nervous filaments are collected, and in them lose their rectilinear parallel direction, so that a new nervous organization probably takes place in them.

Meckel, the first of three generations of famous anatomists of that name in the University of Berlin, proposed in 1751 three functions of the ganglia, namely, to divide a nerve into many fibers, to arrange these fibers according to their site of termination and, finally, to reunite them in larger nerve bundles at their exit from the ganglia. He gave, therefore, the first clear account of what is now understood by the term "nerve plexus," and, although he remarked that the bulk of the nerves leaving a ganglion was much greater than that of the entering nerves, he apparently did not suspect a possible origin within the ganglion of such emergent fibers. Meckel added the significant observation that many nerves of the sympathetic system, especially those leaving the ganglia, were redder and of softer texture than most other nerves, an early glimmering of the recognition of the nonmyelinated nature of the fibers of the "gray rami."

Meckel's views were accepted by Zinn (1755), Scarpa (1779) and Monro (1783), although Monro expressed the belief that "nervous matter" could be furnished by the ganglia and pointed out the close resemblance between the grayish matter of the ganglia and the cortical substance of the brain. It is not evident, however, that he had any clear conception of new nerve fibers arising within the ganglia.

The true meaning of the ganglia remained in obscurity until the beginning of the nineteenth century. Willis' interpretation of ganglia

as "storehouses for animal spirits" had been accepted with a good deal of misgiving by Whytt and had been modified by Lancisi into a conception of "muscular pumps" for accelerating the flow of the spirits to bring about voluntary movement. An entirely opposite view had been advanced by Johnstone, who looked on the ganglia as "filters" for intercepting motor and sensory impressions between "consciousness" and visceral structures, accounting thereby for involuntary motion and for the peculiar sensibility of such parts. Winslow and later Monro had upheld a belief in the independence of the ganglia, comparing them to "small brains," and, lastly, Meckel, followed by Zinn and Scarpa, had postulated that the ganglia were compact "plexuses" for the wide dispersal of fibers to all parts of the body. Such a diffuse and wide distribution of sympathetic fibers has since become an integral part of the present-day conception of the autonomic nervous system. The credit for the first realization of such an arrangement appears to belong to Meckel.

INDEPENDENCE OF THE GANGLIONIC NERVOUS SYSTEM

Xavier Bichat, the son of a physician, was born in 1771. He commenced his medical studies at Lyons and after serving a short period as an army surgeon in the French Revolution began teaching anatomy and physiology in Paris. In 1799 he published his remarkable treatise "Physiologic Researches on Life and Death," and two years later there appeared "Anatomy as Applied to Physiology and Medicine" and the first three volumes of a textbook of descriptive anatomy. His early death, in 1802, robbed physiology of one of its most promising investigators. His ideas were adopted and taught extensively in Edinburgh by Robert Knox, the renowned anatomist. Bichat's writings gave to research on the autonomic nervous system an extraordinary impetus, and his influence was felt in anatomic and physiologic thought almost to the end of the nineteenth century.

Bichat divided life into *la vie organique* and *la vie animale*, a distinction which exists today in the current ideas of "visceral" and "somatic" functions.

> These represent a habitual succession of assimilation and excretion, by which a man transforms continually into his own substance the molecules of neighboring bodies and later rejects these molecules when they have become heterogenous. He lives only in himself through this class of functions; through the other he exists outside himself, he is the inhabitant of the world and not, like a plant, of the place where he was born. He feels and perceives that which surrounds him; he reflects his sensations, voluntarily deceives himself according to their influence and usually can communicate by voice his desires and his fears, his pleasures and his sufferings. I mean by organic life the totality of the functions of the first

class . . . The united functions of the second class constitute animal life, so-called because it is the exclusive attribute of the animal kingdom.[3]

Bichat must be followed closely, since he was the first to correlate the autonomic nervous system with the metabolic functions of the body. He commenced by pointing out the extraordinary symmetry which existed in the external form of the parts belonging to the animal life (e. g., the eyes, ears, limbs, cranial and spinal nerves, etc.) in contrast to the irregularity and central position of the parts belonging to the organic life (e. g., the abdominal and thoracic viscera and the plexuses of the ganglionic nervous system). Furthermore, a continuity of action appeared in the organic life as compared with an intermittent motivation in the animal life. The continuous activity on the part of the organic life consisted of two kinds, assimilation and decomposition and excretion—*l'un compose . . . l'autre décompose.*

Bichat stressed the control of the animal life by the "will" and the influence of fear, anger, joy, etc., on the circulation, respiration and functions of the digestive tract and secretory glands. The center of focus for the animal life was in the brain; that for the organic life lay in the epigastrium and was intimately associated with the complex network of nerve plexuses which occur in this region. Bichat closed his argument on a morphologic note, drawing an analogy between the greater importance in lower animals of the organic life as compared with the animal life and the low development of the brain in these beasts as compared with the extensive sympathetic plexuses.

This conception of visceral as distinct from somatic function is unquestionably Bichat's greatest contribution to the physiology of the autonomic nervous system. The deduction from this general principle which led to his distinction of the sympathetic ganglia as nerve centers entirely independent of the central nervous system was perhaps less fortunate, though throughout his descriptions one can find the seeds of truth which were to flower in the final elucidations of Gaskell and Langley.

Bichat asserted that there is no such nerve as that designated by the term "sympathetic" and that that which was taken for a nerve was noth-

3. Les unes se composent d'une succession habituelle d'assimilation et d'excrétion; par elles il transforme sans cesse en sa propre substance les molécules des corps voisins, et rejette ensuite ces molécules, lorsqu'elles lui sont devennes hétérogènes. Il ne vit qu'en lui, par cette classe de fonctions; par l'autre, il existe hors de lui, il est l'habitant du monde, et non, comme le végétal, du lieu qui le vit naître. Il sent et aperçoit ce qui l'entoure, réfléchit ses sensations, se ment volontairement d'après leur influence, et le plus souvent peut communiquer par la voix, ses désirs et ses craintes, ses plaisirs ou ses peines. J'appelle *vie organique* l'ensemble des fonctions de la première classe . . .les fonctions réunies de la seconde classe forment la *vie animale,* ainsi nommée parce qu'elle est l'attribut exclusif du règne animal.

ing more than a series of communications between nerve centers, placed at varying distances from each other. Disseminated in different regions of the body, the ganglia all possessed independent and isolated action. Each was a focus from which emerged numerous branches to the particular organ or tissue innervated. Some of these fibers passed from one ganglion to another, thus composing in their aggregate a continuous cord.

The nerves were therefore divided by Bichat into two great systems: the one emanating from the brain and spinal cord, the other from the ganglia; the first possessing a single center and associated with volition and sensory impressions from the external world, the second having a number of centers and associated with digestion, circulation, respiration and secretion, in both their anabolic and their catabolic phases. Bichat has been credited with the introduction of the term "vegetative nervous system," but this distinction strictly belongs to Reil, who expounded and developed many of Bichat's views. Bichat himself used the term *système des ganglions* to designate the nerves governing the organic life and was therefore more properly the originator of the name "ganglionic nervous system."

Bichat did not overlook the rami communicantes and even noted the white appearance of some of them in contrast to the gray and soft nature of the fibers emerging from the ganglia. In spite of the fact that he grouped the white rami with the central nervous system, he clearly did not recognize their true significance and looked on them as communicating branches of obscure function between the two great systems.

Reil (1807) followed Bichat in considering the sympathetic ganglia to be independent centers of nervous energy. The rami communicantes, the connections between the animal and the vegetative nervous system, according to Reil, served as semiconductors (*Halbleitung*). Thus, the sensory impressions from the vegetative sphere ordinarily remained in this region and were not communicated to the brain, but in disease the conductivity of the communicating nerves became increased and sensory impressions from the viscera could be transmitted to the sensorium (or level of consciousness). The analogy of a "make-and-break" key between the cerebral and the vegetative nervous system perhaps best explains Reil's conception of the function of the rami communicantes, a view singularly reminiscent of the hypothesis advanced by Johnstone.

Among Bichat's writings appears a passage of significance in that it heralds the discovery of the vasomotor nerves a half-century later.

> The nerves of the ganglia are distributed everywhere to the circulatory system; they seem to exist for it and to belong to it exclusively. It is only with the arteries

that they are introduced into the organs, or rather it is only to the arteries that they are distributed directly, no matter where they are, and the tissue of the organs receives only rare and isolated branches . . . This constant connection between the nervous system of the ganglia and the circulatory system is observed even in the heart, because, as has been noted, the cardiac nerves are all seen either at the origin of the large arterial vessels or along the course of the coronary arteries and do not properly belong to the muscular fibers that compose the heart. Undoubtedly, this incontestable anatomic fact cannot lead one to fix the functional relation that exists between the two systems in question, because the positive properties of the nerves of the ganglia are not known. But one must conclude at least that there remains here an important and essential breach in physiology, for it is reasonable to think that two systems constantly united exist for each other and are necessary to each other, and if the mode of their mutual correspondence cannot be determined, only the adequacy of the means can be blamed.[4]

CONTRIBUTION OF HISTOLOGY

Bichat's functional concepts gained credence steadily during the first half of the nineteenth century, but his belief that the ganglia represented structurally distinct units, giving rise to new nerve fibers, met with opposition, notably from Wützer (1817), Lobstein (1823) and Philip (1817). The finer structural details of the nervous system had still to be disclosed. Although microscopic construction had begun in the early part of the seventeenth century, progress had been slow, and in the eighteenth and the beginning of the nineteenth century microscopic studies were still carried out with simple instruments and by teasing preparations in alcoholic and aqueous solutions. The technic was inevitably crude, and the results were often untrustworthy, so much so that Bichat emphatically refused to use the microscope, in the belief that it gave rise merely to fallacies and delusions. The nineteenth century saw the growth of histology into a separate branch of scientific

4. C'est que les nerfs des ganglions se distribuent par-tout au système circulatoire, paroissent exister pour lui et lui appartenir exclusivement. C'est avec les artères seulement qu'ils s'introduisent dans les organes, ou plutôt c'est aux artères seules qu'ils se distribuent immédiament quelque part qu'elles se trouvent, et le tissu des organes n'en reçoit que quelques remeaux rares et isolés . . . Ce rapport constant entre le système nerveux des ganglions et le système vasculaire, se remarque même sur le coeur; car, comme nous l'avons vu, les nerfs cardiaques se trouvent tous soit a l'origine des gros troncs artériels, soit sur le trajet des artères coronaires, et n'appartiennent point proprement aux fibers musculaires dont le coeur est composé. Sans doute ce fait anatomique incontestable ne peut nous conduire à fixer le rapport de fonctions qui a lieu entre les deux systèmes dont il s'agit, puisqu'on ne connoit point les propriétés positives des nerfs des ganglions. Mais nous devons en conclure au moins qu'il reste ici, en physiologie, une lacune importante et éssentielle: car il est raisonnable de penser que deux systèmes constamment réunis ensemble, existent l'un pour l'autre, sont nécessaires l'un à l'autre, et que si nous ne pouvons déterminer le mode de leur correspondence mutuelle, nous ne devons nous en prendre qu'à l'insuffisance de nos moyens (Bichat, 1802).

investigation. With the gradual refinement of the microscope, the introduction of the microtome by His in 1870 and the elaborate development of staining methods, the intricate pattern of the nervous system began to unfold under the keen eyes of such men as Henle, Kölliker, Ranvier, Golgi and Ramón y Cajal. In 1831 Robert Brown discovered the cell nucleus, and in the succeeding years Schleiden and Schwann developed the cell theory, which formed the basis of all subsequent biologic research.

Ehrenberg (1833) gave the first description of cell bodies in sympathetic and spinal ganglia and the earliest histologic differentiation of nerve fibers into *Gliedernerven,* with a single contour, and *Röhrennerven,* possessing an additional sheath of *Marksubstanz* and therefore having a double contour. In both the sympathetic and the spinal ganglia, in human and animal material, he described irregular corpuscles, *"die mehr einer Drüsensubstanz ähnlich sind,"* apparently not realizing the significance of his discovery. In 1836 Valentin gave a more detailed account of the sympathetic ganglia, describing the cell structure and the nucleus, nucleolus and capsule surrounding each ganglion cell. He noted the difference between the white and the gray rami communicantes and expressed the belief that the white rami arise from the spinal cord and pass to the sympathetic system; he distinguished further between fibers passing through and those ending in the ganglia.

Two years later Remak gave the first adequate description of the unmyelinated nerve fibers, naked axis-cylinders with small varicosities, which he postulated arose from the ganglion bodies of Ehrenberg. Such fibers were believed by Remak to exist exclusively in the ganglionic or sympathetic nervous system, and following Bichat's teaching Remak gave them the name "organic" fibers. In the following year Valentin disputed the nervous nature of Remak's organic fibers, believing them to be prolongations of the capsule around each ganglion cell, which he had observed earlier.

Bidder and Volkmann (1842) also opposed the concept that Remak's fibers were truly nervous, but argued that it was possible to distinguish a nerve fiber peculiar to the sympathetic nervous system. They made the first attempt to measure accurately the caliber of the nerve fiber, a method which ultimately led to Gaskell's fundamental observations. Bidder and Volkmann measured the nerve fibers in the sympathetic trunk and all the ventral and dorsal spinal roots of frogs, and on the basis of their calculations they distinguished two types of nerve fibers, fine myelinated or "organic" and large myelinated or "animal" fibers.

The true nature of Remak's fibers remained in dispute for many years, but gradually they were accepted when Müller, Schwann and

Henle confirmed Remak's observations. Of the function of the rami communicantes several views had arisen: first, the theory that they represented the only origin of sympathetic nerves from the spinal cord (Valentin); second, the theory that they were pathways for sympathetic fibers arising entirely in the ganglia and passing both peripherally along spinal nerves and centrally into the spinal cord along ventral and dorsal roots, and third, a theory, supported by Müller, based on the reciprocal interchange of fibers between the two great systems of Bichat. Bidder and Volkmann observed that in frogs the great majority of fibers in the rami communicantes course peripherally and the minority, centrally. They argued, therefore, that the origin of sympathetic fibers could not be entirely from the spinal cord and that the ganglia must necessarily be considered the origin of new nerve fibers. At the junction of the ramus communicans with the sympathetic trunk they noted that some fibers ran upward to the cephalic end and others downward to the caudal end of the ganglionic trunk.

The gradual acceptance of Remak's views gave a new basis for distinguishing between Bichat's two systems; one system was composed of "tubular" or "animal" nerve fibers, arising exclusively from the brain and spinal cord; the other, of "gelatinous" or "organic" fibers, which had their origin in the various sympathetic ganglia. Therefore, a specific correlation appeared between structure and function, in support of Bichat's concept.

In 1854 Remak published a full description of the structure and connections of the ganglion cells, an account which reflects the generally accepted views of the middle of the nineteenth century (Müller). Multipolar and bipolar cells were observed in all the sympathetic ganglia, while the spinal ganglia contained only bipolar and unipolar cell bodies. In man and lower animals, according to Remak, each sympathetic ganglion was connected with the corresponding spinal nerve by at least two branches.

The lower branch ("ramus communicans sympathicus s. revehens") was *gray* and soft in texture and contained many fine myelinated and unmyelinated nerve fibers. The latter type arose from the cells in the sympathetic ganglia and were distributed peripherally along the spinal nerve. The upper branch ("ramus communicans spinalis s. advehens") was *white* and of firmer texture and contained myelinated fibers. It could be traced centrally into both the dorsal and the ventral spinal roots. Some of the fibers were thought to arise within the spinal cord and end in the sympathetic ganglion, occasionally passing through one ganglion as a white bundle to end in a ganglion lower or higher in the chain.

Although the difference in color and texture between the gray and the white rami had been recognized for many years, Remak's account is one of the earliest clear descriptions. In spite of an observation by Beck (1846) that the cervical and sacral nerves possess only gray rami, there was still no thought of limitation of the white rami to the thoracic and the upper portion of the lumbar region. The rami communicantes were believed to have connections with both the dorsal and the ventral roots and possessed, therefore, both sensory and motor functions. The muscles innervated were nonstriated and gave rise to "involuntary" motion. A third set of sympathetic fibers were designated as "trophic." These, according to Müller, presided over nutrition and secretion and metabolic processes in general and were presumed to correspond anatomically to the "organic" (nonmyelinated) fibers of Remak. Remak, however, felt no necessity for assuming the existence of specific trophic fibers, for, he stated, the nerves which regulate the caliber of the blood vessels accounted for all the known facts concerning the dependence of metabolic processes on the ganglionic nervous system.

The relationship of the vagus nerve to the sympathetic nervous system was not clear. The Webers (1845) had shown conclusively its inhibitory cardiac effect, but the literature does not indicate that antagonistic action between the vagus nerve and the sympathetic nervous system was recognized, and most authors included the vagus nerve as part of the "organic nervous system." Similarly, the ciliary ganglion, described by Willis in 1683, the sphenopalatine and submaxillary ganglia, described by Meckel in 1748 and 1749, and the otic ganglion, described independently by Brachet and Arnold in 1828, were all regarded as belonging to the ganglionic nervous system.

In 1851 Budge and Waller, in repeating Petit's original experiments, showed that section of the vagosympathetic trunk in the dog was not followed by complete degeneration of the peripheral end of the nerve. There remained an intact bundle which they identified with the sympathetic trunk and traced to the first and second thoracic segments of the spinal cord. On stimulation of this area in the intact animal they obtained dilatation of the pupil, which was abolished unilaterally by section of the cervical portion of the sympathetic trunk. They named the region the "ciliospinal center." In 1857 Meissner gave the first description of the submucous plexus in the intestinal tract, and in 1864 Auerbach published his account of the myenteric plexus of the intestinal wall, which he had discovered two years previously. An important observation by Reissner in 1862 that the fine nerve fibers were present in the anterior roots of the thoracic region in far greater numbers than elsewhere in the spinal segments passed unnoticed, but the ground was

already laid for the work of Gaskell and Langley. In the meantime physiology had contributed the proof for the existence of vasomotor nerves.

DISCOVERY OF VASOMOTOR NERVES

Johannes Müller, in 1838, had recognized two kinds of muscles, the striated and the nonstriated, the latter being represented in the iris, uterus, bladder and gastro-intestinal tract. There was still considerable doubt whether arteries possessed a true muscular coat, but Henle, in 1840, noting that sympathetic fibers, apparently motor in nature, were distributed particularly along blood vessels, was led to the conclusion that the middle coat of the arteries is muscular. Histologic proof of this arrangement was given by von Kölliker in 1846. The ground was thus prepared for Claude Bernard's discovery of the vasomotor nerves.

Bernard began the study as an investigation of the influence of the nervous system on body temperature. It seemed likely that chemical changes between the blood and the tissues would determine the development of heat, and since the sympathetic nerve fibers so often accompanied the blood vessels Bernard began his investigations with the sympathetic nervous system. For several years he had been studying the cervical portion of the sympathetic trunk in relation to pupillary changes, and his attention having been focused on the eye, the accompanying vascular changes were at first overlooked.

The results of Bernard's first researches on the effect of section of the cervical portion of the sympathetic trunk on the blood vessels of the head appeared in December 1851. In March 1852 his second paper described in greater detail the increase in the blood flow and in the temperature of the skin on the side of the head on which he had sectioned the sympathetic trunk in the neck.

> All the part of the head which becomes hot after section of the nerve becomes also the seat of more active circulation. The arteries especially seem fuller and appear to pulsate more forcibly; this is distinctly seen, in the rabbit, in the vessels of the ear.

Foster wrote:

> In Bernard's mind the importance of his experiments on the sympathetic lay in the proof which they afforded that the nervous system directly acted on the chemical changes in the tissues and so intervened in the development of heat; the vascular phenomena he regarded as of secondary importance.

The first evidence of the suspected vasomotor function of the sympathetic nervous system was confirmed almost immediately by Brown-Séquard, who grasped the significance of the result, namely, that section of the cervical portion of the sympathetic trunk led to paralysis and therefore to dilatation of the blood vessels. In August 1852 Brown-

Séquard published in Philadelphia the corollary proof—that galvanic stimulation of the cervical portion of the sympathetic trunk led to constriction of the blood vessels, diminution in blood flow and decrease in the temperature of the skin in the area supplied. His account of this discovery follows:

> Led by experiments that I had made several years before, with my friend Dr. Tholozan, on the influence of nerves on blood vessels, I understood at once that the fact discovered by Professor Bernard was due to the paralysis of the blood vessels after the section of the sympathetic; and I thought that, if this view were right, I should find galvanization of this nerve producing the reverse of the effects of the section. The experiment being made, I found, as I had foreseen, that the blood vessels contracted, and that the quantity of blood and the temperature diminished.

In November 1852 Bernard, unaware of Brown-Séquard's experiments, announced the same results from stimulation of the cervical portion of the sympathetic trunk, and in 1853 these results were confirmed independently by Waller in England and Budge in Germany. Bernard (1862), Schiff (1862) and von Cyon (1868) showed the same vasoconstrictor action of the sympathetic supply to the upper limb, and Bernard (1854) and Ostroumoff (1876) obtained further confirmation in the lower limb.

The foundations of the conception of a universal vasoconstrictor action of sympathetic nerve fibers were thus laid, but several years elapsed before an active vasodilator effect was definitely established. In 1851 Ludwig's classic paper was published on the increased secretion of saliva on stimulation of the chorda tympani nerve. This result was confirmed and extended by Czermak, but the attendant vascular phenomena in these experiments had not been stressed. In 1858 Bernard showed that the blood supply of the submaxillary gland is under the control of two types of nerve fibers—the sympathetic, stimulation of which produces constriction of the arteries and diminution in blood flow, and the chorda tympani, stimulation of which gives rise to dilatation of the arteries and full and rapid circulation. In 1876 Stricker demonstrated the vasodilator effect of stimulation of the dorsal spinal roots, and in 1880 Dastre and Morat produced evidence for the existence of vasodilator fibers to the mucous membrane of the gums and palate in the cervical portion of the sympathetic chain.

The credit for the discovery of the vasomotor nerves goes in a large measure to Bernard, though to the end of his life he persisted in the belief that the increase in the temperature of the skin on stimulation of the sympathetic nervous system could not be entirely explained on the grounds of vascular change but held that the sympathetic fibers directly controlled the metabolic processes.

Bernard regarded the ventral spinal roots as the origin of the efferent sympathetic fibers giving rise to involuntary movements of the gastrointestinal tract, iris, bladder and uterus, to the constriction of blood vessels, to the increase in salivary secretion and to changes in metabolic activity of the tissues. That afferent fibers existed in the sympathetic system was by now generally accepted. "On voit," wrote Bernard, "qu'il faut admettre des filets sensitifs centripètes dans le système sympathique comme dans le système cérébrospinal." ("It is evident that the existence of the centripetal sensory fibers must be admitted in the sympathetic as well as in the cerebrospinal system.") It was granted that the viscera are ordinarily incapable of giving rise to sensory impressions of a conscious nature, but they were thought to possess a particular type of sensibility, *sensibilité réflexe*. The basic principles of the reflex arc were worked out, in particular by Hall (1856), and Bernard considered such afferent fibers of the sympathetic system to be the afferent limbs of reflex arcs. According to Bichat, the reflex takes place through the sympathetic ganglia and independently of the cerebrospinal nervous system, but Bernard opposed this view and expressed the belief that all sympathetic reflexes take place through the spinal cord.

Bernard opened another door to the discovery of the "organic" nervous system, for interest in a central representation of this system can, without doubt, be traced to his classic experiment on puncture of the floor of the fourth ventricle. Foster gives the following account of Bernard's approach to the problem:

> Regarding, as he had come to do, the appearance of the sugar as a secretion —an internal secretion of the liver—he argued that this secretion, like other secretions, would be subject to the influence of an appropriate nerve. Anatomical considerations, as well as earlier observations on the vagus, and its relations to digestion, led him to suppose that the nerve in question could be none other than the vagus nerve. And he was confirmed in this view by the fact which he had early ascertained that section of the vagus nerves did away with the formation of the sugar. He accordingly expected to find that galvanic stimulation of the vagus trunks would lead to an increase of the hepatic sugar; but in this he was grievously disappointed; all his results were negative. Remembering, however, some older experiments of his on the fifth pair, in which he had produced secretory effects—tears and saliva—by irritating the nerve in a special way, namely, by puncturing it at its origin in the brain, he conceived the idea of applying the same method to the vagus at its origin in the floor of the fourth ventricle.

Bernard found that small punctures in the floor of the fourth ventricle between the origin of the vagus and that of the auditory nerve gave rise to polyuria, glycosuria and albuminuria. The phenomena were transient, persisting usually for only twenty-four hours; they appeared to be independent one from another and could be produced separately, according to the exact site of the puncture. Lesions in the anterior end

of the fourth ventricle, just in front of the origin of the fifth pair of cranial nerves, produced a great increase in salivation. Bilateral section of the vagus nerve or of the cervical portion of the sympathetic trunk failed to prevent the appearance of glycosuria after *piqûre*. Bernard expressed the belief that the results were partly explicable on a basis of circulatory changes in the viscera, and the attention of physiologists was thus focused on a possible vasomotor center in the medulla. The search for higher centers of control followed as a logical result.

BASIS OF THE PRESENT-DAY CONCEPTION

Schenk and Birdsall, in 1880, and Balfour, in 1881, demonstrated in fish, chick and human embryos that the first trace of the sympathetic system appears as short branches from the spinal nerves, terminating in small irregular cellular masses. These masses were at first unconnected with each other, but each was attached to the spinal ganglion by a small communicating branch. Later in development, the groups of cells sent commissural branches to each other, thus forming the ganglionic chains, and branches to the periphery to form the sympathetic plexuses. When, in 1884, Onodi confirmed these earlier observations and established clearly that the primordia of the sympathetic system arose and migrated from the primitive spinal ganglia, the theory of complete independence of the ganglionic nervous system, as advocated by Bichat, began to break down.

Gaskell's first results appeared as a preliminary communication to the Physiological Society (Great Britain and Ireland) in February 1885 and were published in full the following year. The paper proved a landmark in the history of the investigation of the sympathetic system. Gaskell studied serial sections through the ventral and dorsal spinal roots and the rami communicantes of the dog after staining by the osmic acid technic, then recently introduced by Schultze. Since the development of the silver impregnation methods, many of Gaskell's original observations have proved incorrect, but his fundamental conclusions have remained and have formed the structural basis of present-day views.

Gaskell observed no unmyelinated fibers in the ventral roots, and he believed that those in the dorsal roots were solely peripheral branches to the spinal meninges and that none entered the spinal cord itself. He therefore asserted that no unmyelinated fibers leave the central nervous system in either the ventral or the dorsal roots and that all such fibers are branches of cells lying in the sympathetic ganglia. The gray rami are therefore composed entirely of peripheral branches from the lateral chain of ganglia. The only possible communication between the organic and the animal nervous system remained in the white rami.

Gaskell next turned his attention to the myelinated fibers and noted in the ventral roots of the cervical region myelinated fibers, none less than 3.6 microns in diameter. In the ventral root of the second thoracic nerve appeared a sudden large influx of medullated fibers of smaller caliber, from 1.8 to 2.7 microns in diameter. Such bundles of exceedingly fine medullated fibers existed in the ventral roots throughout the thoracic region and caudally as far as the third lumbar segment. Below this level the small medullated fibers disappeared from the ventral roots.

The significance of the fine myelinated fibers became evident when Gaskell traced them into the white rami communicantes and showed that the white rami are composed almost entirely of such fibers. The white rami were thus clearly limited to the thoracic and upper lumbar segments and became definitely associated with an outflow of nerve fibers from the spinal cord through the ventral roots.

In the cephalic portion of the sympathetic chain the same bundles of small medullated nerve fibers could be followed as far as the superior cervical ganglion, beyond which they could be traced no farther, and caudally they formed the lumbosacral portion of the sympathetic trunk, gradually decreasing in number until in the lower sacral regions they ultimately disappeared. In a lateral direction many fine myelinated fibers were traced through the sympathetic ganglia into the splanchnic nerves.

In the second and third sacral ventral roots Gaskell again noted medullated fibers of fine caliber, which he traced into the nervi erigentes. There were similar finely myelinated nerve fibers in the spinal accessory, vagus, glossopharyngeal and chorda tympani nerves. There appeared, therefore, to be three separate outflows of fine medullated fibers from the central nervous system to peripherally situated motor ganglion cells —"bulbar," "thoracolumbar" and "sacral." This was Gaskell's fundamental conception of the visceral and vascular nerves in 1886. The motor function of sympathetic nerves had long been associated with involuntary motion, and Gaskell later (1916) used the term "involuntary nervous system," "meaning thereby a system of motor nerve cells to involuntary structures, which have left the central nervous system and have migrated out to a greater or lesser distance."

The ordinary sensory nerves of the skin proved to be of the larger medullated type. Gaskell therefore considered it reasonable that the large medullated fibers of the involuntary nervous system were of the same nature. He looked on them as passing through the ganglionic chain without interruption and in all probability as arising in the nerve cells of the dorsal spinal ganglia. Gaskell considered the involuntary nervous system as purely a motor or effector mechanism. He tended

to limit the term to the peripherally lying neurons, referring to the outflow from the neural axis as "connectors," but the limitation presented obvious difficulties and was not rigidly held.

He noticed that the lateral horn of spinal gray matter formed a distinct column of cells in all parts of the cord, except in the cervical and lumbar enlargements, where it became indistinguishable. Clarke's column of cells had a similar distribution in a longitudinal direction. The close correspondence of the cell columns to the segments from which arose the fine medullated fibers led Gaskell in 1886 to postulate that the cells in the lateral horn and in Clarke's column were the origin of such fibers. It was not until the discovery of the cell changes following axonal division that the sympathetic outflow from the cord was limited to the cells of the lateral horn.

At first, Gaskell was inclined to lay emphasis chiefly on the cells of Clarke's column. He supposed that each spinal segment gave rise to two "roots," a "somatic" root, composed of two parts, a ganglionic portion arising from the dorsal horn and a nonganglionic portion from the ventral horn of gray matter, and a "splanchnic" root, associated with visceral and vasomotor functions. It was divisible, likewise, into two parts, a ganglionic portion, arising from Clarke's column of cells, and a nonganglionic portion, arising from the cells of the lateral horn.

The nonganglionated portions of both the somatic and the splanchnic root passed directly without interruption to their terminations in striated muscle, whether somatic or visceral. Thus, Gaskell linked the nonganglionated part of the splanchnic root with the lateral or "respiratory" roots, described by Bell. The muscles innervated included those of mastication, deglutition, phonation and respiration. Gaskell's definition of "somatic" and "splanchnic" was later misinterpreted to mean the fibers to "striated" and "nonstriated" muscles, respectively, and led to misunderstanding of his conclusions.

Of the function of sympathetic ganglia Gaskell, in 1886, offered the following view:

> Each nerve fibre leaves the central nervous system as a fine medullated nerve fibre which passes directly into its appropriate ganglion, and there in consequence of communication with one or more of the ganglion cells loses its medulla and passes out not as a single non-medullated fibre but as a group of non-medullated fibres. Such ganglion cells not only assist in the conversion of a single nerve fibre into a group of fibres but at the same time are centres for the members of the group in so far as they possess a nutritive power over them; they are not however centres in the sense of being capable of reflexly setting these fibres into activity; a conclusion which is self-evident if each nerve cell is connected only with nerve fibres possessing the same function.

Gaskell was probably the first to postulate the existence of two antagonistic systems of nerves for the control of involuntary muscu-

lature and glandular secretion, one excitatory and the other inhibitory. The vagus nerve, as the inhibitory cardiac nerve, he regarded as having anabolic action, in contradistinction to the catabolic effect of the sympathetic innervation. To Gaskell the sympathetic system was clearly the catabolic agent and the cerebrospinal system probably the anabolic, and in Gaskell's concluding remarks one finds the link between Bichat's "organic" nervous system and Langley's subsequent classification into "sympathetic" and "parasympathetic" divisions. Gaskell wrote in 1886:

> The evidence is becoming daily stronger that every tissue is innervated by two sets of nerve fibres of opposite characters so that I look forward hopefully to the time when the whole nervous system shall be mapped out into two great districts of which the function of the one is katabolic, of the other anabolic, to the peripheral tissues: two great divisions of the nervous system which are occupied with chemical changes of a synthetical and analytical character respectively, which therefore in their action must show the characteristic signs of such opposite chemical processes.

Gaskell's generalization concerning the involuntary nervous system and the formulation in 1891 of the neuron theory of Waldeyer resulted in an entirely new orientation of ideas. In 1874 Langley began his researches on the mechanism of secretion of the submaxillary gland, and after investigation of the action of drugs he was led naturally to a study of the presumed secretory nerve fibers. In 1889 he began his work on the effect of nicotine on nerve cells, and thereafter until his death, in 1925, his numerous publications (listed in full by Fletcher [1926]) dealt largely with different aspects of the autonomic nervous system.

Hirschmann, in 1863, had shown that after a moderate dose of nicotine, stimulation of the sympathetic trunk in the neck caused no dilatation of the pupil, and he concluded that nicotine paralyzed the endings of the dilator fibers in the pupil. Heidenhain (1872) confirmed this observation after intravenous injection of nicotine, and in 1889 Langley and Dickinson showed that after such a procedure stimulation of sympathetic fibers above the superior cervical ganglion still caused dilatation of the pupil and constriction of the vessels in the ear of a rabbit, although stimulation below the ganglion failed to produce these effects. They therefore concluded that nicotine acts by paralyzing the cells of the sympathetic ganglia, and by their experiments established that the dilator fibers for the pupil and the vasoconstrictor fibers for the ear end in cells in the superior cervical ganglion.

By applying this discovery to other parts of the body Langley was able to map out the cell stations and areas of distribution of most of the "preganglionic" and "postganglionic" neurons, which he thus named in 1893. In 1898 he introduced the term "autonomic nervous system"

to include the cranial, thoracolumbar and sacral outflows, qualifying his suggestion with the following explanatory note:

> The word "autonomic" does suggest a much greater degree of independence of the central nervous system than in fact exists, except perhaps in that part which is in the walls of the alimentary canal. But it is, I think, more important that new words should be used for new ideas than that the words should be accurately descriptive.

He expressed the belief that the cells of the Meissner and Auerbach plexuses were in the course of the bulbar and sacral outflows, but since he had no clear proof of such an arrangement he placed them in a class of their own as the "enteric nervous system" (1900).

Langley sectioned the dorsal spinal root distal to the ganglion and observed, after the requisite time for degeneration, that all, or all but a few, of the medullated fibers in the corresponding white ramus degenerated. Section of the sympathetic trunk or of the splanchnic nerve did not cause this degeneration. In the belief that all visceral afferent fibers were medullated, Langley concluded that the cell stations for the visceral afferent fibers lay in the dorsal root ganglia and that such fibers entered the root by the white ramus. He was therefore led (1903) to regard the autonomic nerves as purely motor and the afferent nerve fibers accompanying them as indistinguishable anatomically from other afferent nerves.

The discovery of epinephrine by Oliver and Schäfer in 1893 was followed almost immediately by the demonstration of the similarity of its effect to that of sympathetic stimulation. Lewandowski (1899) was the first to show that intravenous injection of adrenal extract caused the typical sympathetic responses in the eye (widening of the pupil, retraction of the nictitating membrane, elevation of the upper eyelid and exophthalmos). Extirpation of the superior cervical ganglion elicited the reaction better. The universal association of epinephrine and sympathetic innervation and the important phenomena of sensitization of smooth muscle in general by sympathetic ganglionectomy were established beyond question by Langley (1901) and two of his pupils, Anderson and Elliot.

The discovery that the effects produced by epinephrine are confined to parts which are or have been innervated by fibers from the thoracolumbar (sympathetic) outflow and that other drugs, such as pilocarpine, cause effects similar to those produced by stimulation of fibers in the cranial and sacral outflows led Langley in 1905 to group the latter fibers under the name "parasympathetic nervous system."

> The facts that the sympathetic innervated the whole body, whilst the cranial and sacral outflows innervated parts only, and that the sympathetic had, in general, opposite functional effects from those of the other autonomic nerves, indicated that the sympathetic was a system distinct from the rest.

Langley's achievements in the field of the autonomic nervous system are too recent to need further comment. In the words of Fletcher:

> They stand permanently in their place not merely as additions here and there to knowledge, but as indispensable stepping stones along which, at this point or that, the progress of knowledge has actually made its way. Each gain he made was a step placed securely and finally, and few indeed of them as the road has become more firmly and widely trodden by others following, have been found wrongly placed. All his chief works keep, and must always keep, their place in the significant history of animal physiology.

MODERN TRENDS

The extensive development in the field of surgical treatment of disorders of the peripheral sympathetic nerves and the perfection of intracranial exploration have revealed the wide gaps that still exist in knowledge of the autonomic nervous system. The surgical approach in the relief of vasospastic phenomena has led to realization of the importance of extending Langley's careful localization of the postganglionic cells in lower animals. The sudden respiratory and cardiac embarrassments and other autonomic nervous phenomena during cerebral manipulation have emphasized the need of more careful study of the central connections of this system. Much has been done along this line since the early observations of Bernard, Goltz and Karplus and Kreidl, and a controlling mechanism for visceral and vasomotor functions, still inadequately understood, has been established in the medulla, in the hypothalamus and, more recently, in the cortex.

The interconnections and extensive distribution of the neurons of the sympathetic division, with their diffuse discharge, have been contrasted with the arrangement of the neurons of the parasympathetic division for specific action, and the characteristic antagonistic effects of these two divisions of the autonomic system have become more evident. The underlying basis of emotional behavior and the explanation for many of the "sympathies" are at last being revealed through the brilliant studies of Cannon.

With the discovery of the elaboration of chemical substances, sympathin (Cannon) and acetylcholine (Loewi and Dale), at the terminations of sympathetic and parasympathetic nerve fibers, respectively, the first important links between the autonomic and the endocrine system are being welded. This interrelationship will unquestionably loom larger in the future, and one can confidently look forward to a clearer understanding of both systems through the rigorous pursuit of this phase of research. It will assuredly lead back to Bichat—to his early realization of the nervous control of metabolic processes; to Bernard—to the means of this control through the vasomotor system, and to the goal of achievement, the maintenance of a constant internal equilibrium for the life of the organism.

The stability of the *milieu intérieur* is the primary condition for freedom and independence of existence; the mechanism which allows for this is that which ensures in the *milieu intérieur* the maintenance of all the conditions necessary to the life of the elements . . . These are the same conditions as are necessary for life in simple organisms; but in the perfected animal, whose existence is independent, the nervous system is called upon to regulate the harmony which exists between all these conditions.[5]

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5. La fixité du milieu intérieur est la condition de la vie libre, indépendante; la mecanisme qui permit est celui qui assure dans le milieu intérieur le mainien de toutes les conditions nécessaires à la vie des éléments . . . Ce sont les mêmes conditions que celles qui sont nécessaires à la vie des êtres simples; seulement chez l'animal perfectionné à vie indépendante, le système nerveux est appelé à régler l'harmonie entre toutes ces conditions (Bernard, 1878).

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Abstracts from Current Literature

Anatomy and Embryology

THE THALAMIC PROJECTION TO THE CENTRAL GYRI IN MACACUS RHESUS. A. EARL WALKER, J. Comp. Neurol. **60**: 161 (Aug.) 1934.

The general consensus is that the fillet ends in the ventral nucleus of the thalamus. The object of this study was to see where the thalamic projections from this nucleus end. This was done by making incisions in numerous precentral and postcentral convolutions in the brains of monkeys and observing the degeneration in the thalamic nuclei. Serial sections were made of the thalamus and cortex to show the exact extent of the lesion. Four cases are reported.

A large area of destruction in the cortex of the frontal and parietal opercula produced complete degeneration of the pars inferior of the nucleus ventralis posteromedialis (arcuate nucleus). A circumscribed lesion of the middle portion of the precentral and postcentral convolutions produced a well defined complete degeneration in the pars superior of the nucleus ventralis posteromedialis. A small lesion of the superior portion of both precentral and postcentral convolutions produced a well defined lesion in the lateral portion of the nucleus ventralis posterolateralis. A large lesion of the cortex of the lateral surface of the left hemisphere involving a portion of the occipital lobe, the angular and supramarginal gyri and a small part of the adjacent parietal region and a lesion along the medial surface of the hemisphere undermining the cortex of the paracentral lobule produced two large areas of degeneration, one in the pulvinar and another in the lateral portion of the ventral nucleus. Thus, in general, Walker has destroyed areas in the face region, the arm region and the leg region of the somatosensory area and has found lesions from the medial to the lateral portion of the ventral nucleus, which suggests a horizontal segmental thalamic representation of the body segments. The ventral nucleus appears to be the main source of projection fibers to the rolandic area, which is believed to be the primary somatosensory region in Macacus rhesus.

FRASER, Philadelphia.

THE DEVELOPMENT OF THE MOTOR NUCLEI OF THE HINDBRAIN OF THE CHICK, GALLUS DOMESTICUS. LISGAR BOWNE ECKARDT and RUSH ELLIOTT, J. Comp. Neurol. **61**:83 (Feb.) 1935.

This paper presents the results of a study of the development and organization of the motor nuclear groups of the hindbrain of the domestic fowl during the entire period of incubation. Embryonic structures have been compared with those in the adult, so that the time of acquisition of the adult plan of structure could be noted. Transverse sections of the brain were stained with Heidenhain's iron hematoxylin stain. The ventral motor nucleus of the twelfth nerve was seen first in the 5 day embryos. The dorsal motor nucleus of the twelfth nerve was established in the 6 day embryos. Two components of the motor nucleus were recognized: a larger one, the dorsal motor nucleus of the tenth nerve and a smaller, ventrally placed one, the pars vagi component of the nucleus intermedius. An indication of the first can be seen at the fifth day. The motor nucleus of the seventh nerve was also seen at the fifth day, as was that of the chief motor nucleus of the sixth nerve. The accessory nucleus of the sixth nerve appears first at the seventh day. Only two nuclei giving origin to the fifth nerve were observed.

FRASER, Philadelphia.

HISTOLOGICAL ANALYSIS OF THE NISSL-PATTERN AND SUBSTANCE OF NERVE CELLS. LÁRUS EINARSON, J. Comp. Neurol. **61**:101 (Feb.) 1935.

The problems considered in this paper are whether the pattern of the Nissl bodies is a more or less rigidly constant precipitation or coagulation pattern of

the cytoplasm of nerve cells, regardless of the nature of the p_H of the fixative used, and whether there is definite evidence that Nissl bodies themselves are composed of two or more histologic elements. All material was taken from rabbits—Purkinje cells, large motor cells of the medulla oblongata and spinal and sympathetic ganglia. Many varied fixatives with known p_H values were used.

Einarson believes that the pattern of the Nissl bodies is little modified by varying the fixative and that only the capacity of the cells for being stained with ordinary dyes is modified and changed by the selection of the fixative. He interprets the differences of the condition of the Nissl substance as evidence of different physical states within the cytoplasm previous to fixation. He concludes that within the limits of normal functional changes (chromophilia and chromophobia) the patterns presented by the Nissl bodies represent more or less rigidly constant precipitation patterns of nerve cells, regardless of variety and of the p_H of the fixative, and that in the protoplasm of the living nerve cell there exist at least two colloidal substances: One is a fluid which represents the dispersed phase and after coagulation constitutes the Nissl bodies. The other is a highly viscid semisolid or plastic substance of considerable density, which represents the continuous phase. The Nissl bodies contain at least three histologic components: (*a*) a basophilic chromatin substance; (*b*) basophilic protein and (*c*) acidophilic protein. The basophilic protein is soluble in warm water, while the basophilic chromatin and the acidophilic protein are insoluble. The basophilic chromatin and protein are soluble in acids and in a solution of sodium carbonate, while the acidophilic protein is insoluble.

FRASER, Philadelphia.

DEVELOPMENT OF THE SENSE ORGANS OF THE LARVA OF BOTRYLLUS SCHLOSSERI. CASWELL GRAVE and GORDON RILEY, J. Morphol. **57**:185 (March) 1935.

The development of the sense organs of the larva of Botryllus Schlosseri was studied in serial sections of eggs, embryos and early larvae to determine any homologies between its sense organs (statoliths, sensory and glandular papillae and light-sensitive organs) and the structurally different ones of the ascidians Molgula and Ammaroucium. The statolith appeared in the embryo of Botryllus as a single club-shaped cell. The primordia of the light-sensitive organs, each arising from a ganglion cell, developed slightly later, as five small filaments which penetrated the cavity of the statolith. Pigmentation of the statolith and a twisting process, orienting it into position as found in the free-swimming larva, followed. Anterior ectodermal evaginations gave rise to the three tactile papillae, central cells of these differentiating into rod-shaped sensory receptors and ganglion-like masses which established connections with the central nervous system. The results indicated that the statoliths of different ascidian larvae are homologous; the "direction eyes" probably are not but have evolved independently from a light-sensitive area in the primitive larva of a common ancestral ascidian. The sensory papillae of Botryllus have no homologs in the larvae of Molgula and Ammaroucium.

WYMAN, Boston.

SALIVARY GLAND INCLUSION IN THE HYPOPHYSIS. E. V. MÂRZA and V. D. MÂRZA, Rev. franç. d'endocrinol. **12**:479 (Dec.) 1934.

The authors report a rare case of inclusion of salivary gland tissue in the hypophysis. Only two other similar cases are on record, one repoted by Bevaqua in 1911 and the other by Oberling in 1924. The case studied by the authors was that of a girl, aged 18, who died as the result of rupture of the spleen caused by an accident. Of great interest were two small lobules of salivary gland tissue in the posterior lobe of the hypophysis. Each lobule had an excretory duct, which communicated with a large cyst in the intermediary lobe. Each salivary lobule was composed of about thirty or forty serous acini and only one mucous acinus. They were spherical or elongated, with a narrow lumen and a visible membrana limitans

externa; in transverse sections they measured from 30 to 50 microns. The microscopic appearance of the cells was that of normal active salivary cells. Each lobule had its own excretory canal; they all opened into one common duct which communicated with the cyst in the intermediary lobe. The authors believe that the salivary gland inclusions in the hypophysis are probably aberrant shoots carried along with Rathke's diverticulum into the infundibular region.

NOTKIN, Poughkeepsie, N. Y.

THE STRUCTURE OF THE PHRENIC NERVE IN MAN. N. A. MAXIMOVITCH, Sovet. psikhonevrol. **6**:36, 1934.

Maximovitch attempted to follow the collateral branches and the endings of the phrenic nerve. Both the right and the left nerve were examined in seven cases. In the cervical portion of the phrenic nerve there is anastomosis with the sympathetic nerve in three places. There are no branches in the thoracic portion. At the diaphragm the nerve divides into four or five trunks, one of which, the abdominal, penetrates through the diaphragm into the abdominal cavity, where it subdivides into several trunks. One of these loses itself in the adrenal plexus, while the others go to the sympathetic net around the inferior vena cava. The main trunk of the phrenic nerve consists of three types of fibers, medullated, sympathetic and parasympathetic, with a predominance of the medullated fibers of large caliber. The sympathetic fibers run in fascicles of from twenty to thirty fibers, while the parasympathetic fibers run singly and often spirally around the medullated fibers. The branches which end in the diaphragm retain this mixed character to the end, while the abdominal branch consists almost exclusively of sympathetic fibers which terminate in the ganglia of the adrenal plexus.

NOTKIN, Poughkeepsie, N. Y.

Physiology and Biochemistry

HEMORRHAGE IN RELATION TO SHOCK: EXPERIMENTAL EFFECT OF INTRAVENOUS INJECTION OF SALINE, GUM ACACIA, AND BLOOD ON THE RATE OF ADRENAL SECRETION RESULTING FROM HEMORRHAGE. N. E. FREEMAN, Ann. Surg. **101**: 484 (Jan.) 1935.

The condition of shock, far from being evidence of exhaustion of the sympathetic adrenal system, has been demonstrated to be due to overstimulation of that system. The primary effect of this stimulation is to overcome the ill effect of loss of blood and fall of blood pressure, but if persisted in it will lead to still further stasis in the circulation, a decrease in the blood volume and a vicious circle terminating in death. It is essential, therefore, to terminate the hyperactivity of the adrenal glands by restoration of the blood volume, and to do this sufficiently early so that further peripheral stasis does not take place. Freeman's experiments with the denervated heart, a heart that is abnormally sensitive to adrenal secretion, indicate that restoration of the blood volume after a brisk hemorrhage can best be brought about by the transfusion of blood but that 6 per cent acacia in physiologic solution of sodium chloride is an effective substitute, whereas the solution alone is merely a temporary expedient. In a critical experiment, after hemorrhage of only 20 per cent, but in an animal showing all the manifestations of excessive activity of the adrenal-sympathetic system, no significant response on the part of the denervated heart was obtained by injection of physiologic solution of sodium chloride in volume equal to the hemorrhage, followed by injection of half the amount of acacia, whereas the animal was restored to its former condition by the reintroduction of blood. The author concludes: "Adequate treatment of hemorrhage requires an early restoration of the circulating blood volume in order to inhibit the sympathetic activity before further loss of blood volume through stasis shall occur."

FREEMAN, Washington, D. C.

THE COMPOSITION OF TISSUES IN DEHYDRATION. BENGT HAMILTON and RUTH SCHWARTZ, J. Biol. Chem. **109**:745, 1935.

The term dehydration, in the clinical sense, ordinarily is taken to indicate belief that the loss of water plays a specially important part in producing the clinical symptoms observed. Hamilton and Schwartz have studied the effects of withholding water, but allowing food, on the composition of tissues of dogs. They found that loss of extracellular fluid occurred to a large extent, chiefly from muscle tissue, which lost 35 per cent of its water and 22 per cent of its base, and from the skin, which lost 43 per cent of its water and 24 per cent of its base. The extracellular source of this loss was assumed from the fact that the base lost was not potassium. There was no demonstrable loss of potassium from any tissue analyzed, indicating that there was no withdrawal of intracellular water beyond the loss of water without electrolytes which led to a concentration of them in the body fluids. It is of interest to note that in the brain, liver and kidneys decrease in the volume of water in the tissue was slight and the withdrawal of water was not accompanied by a loss of electrolytes. Since the brain, liver and kidneys lost water and not tissue fluids, they differ from the skin and muscle in which loss of tissue fluid occurred.

PAGE, New York.

THE HISTOCHEMISTRY OF THE ADRENAL GLAND: I. THE QUANTITATIVE DISTRIBUTION OF VITAMIN C. DAVID GLICK and GERSON R. BISKIND, J. Biol. Chem. **110**:1, 1935.

Glick and Biskind have employed an ingenious technic originated by Holter and Linderstrøm-Lang to ascertain the distribution of vitamin C in beef adrenal gland. By this method the histologic structure and the chemical composition may be correlated. A comparison was also made of the numbers of cells in the various zones of the cortex and in the chromaffin region of the medulla in order to estimate the relative amount of vitamin C contained in the different types of cells. It was found that vitamin C was present in greatest concentration in the zona fasciculata, especially in its outer portion, where it is composed of densely packed cells surrounding small sinusoids. The method employed in this investigation may be of especial interest to those wishing to correlate certain chemical and histologic aspects of the central nervous system.

PAGE, New York.

THE HISTOCHEMISTRY OF THE ADRENAL GLAND: II. THE QUANTITATIVE DISTRIBUTION OF LIPOLYTIC ENZYMES. DAVID GLICK and GERSON R. BISKIND, J. Biol. Chem. **110**:575, 1935.

The lipolytic enzymes in serial microtome sections of adrenal glands have been determined by Glick and Biskind. These enzymes in the adrenal glands may be of especial importance because, it is believed, they are concerned in the splitting of lipids, which in turn may be concerned in the elaboration of the secretions of the glands. The technic of Linderstrøm-Lang and Holter was employed. This provides a thousandfold refinement of macrotitrations without loss of accuracy. They found that the lipase activity was relatively high throughout the organ, it being especially active in the compact zona fasciculata and zona reticularis of the cortex and the beginning of the medulla. The activity was greatest in the medulla. Esterase is distributed similarly. It is interesting that the medulla contains the least lipid and that the zona glomerulosa, which possesses a relatively high concentration of esterase, is also poor in lipid. Those portions of the adrenal gland containing the highest concentration of lipid-splitting enzymes were poorest in lipid.

PAGE, New York.

STUDIES ON THE PHOSPHORUS COMPOUNDS OF THE BRAIN: I. PHOSPHOCREATINE. STANLEY E. KERR, J. Biol. Chem. **110**:625, 1935.

The work of Gerard and Wallen in 1929 strongly suggested the presence of phosphocreatine in nerve tissue. This substance is highly labile and is known

to be involved in the liberation of energy during muscular contraction. Kerr has now isolated it in crystalline form from the brain of the cat. After death phosphocreatine disappeared from the brain with far greater rapidity than from muscle. For example, brain immersed in liquid air or crushed in tri-chloro-acetic acid within three seconds from the time of excision suffered a loss of 70 per cent of the labile phosphorus. Within ten minutes no phosphocreatine was detected. It disappeared much more slowly from the brain of the frog than from that of the turtle. The hemispheres of the brain and the cerebellum of the cat contain about equal amounts of the substance. The extraordinary lability of phosphocreatine and its participation in reactions involving liberation of energy in vivo add especial interest to its isolation from cerebral tissue.

PAGE, New York.

THE LACTIC ACID CONTENT OF MAMMALIAN BRAIN. BENNETT F. AVERY, STANLEY E. KERR and MUSA GHANTUS, J. Biol. Chem. **110**:637, 1935.

The speed with which phosphocreatine disappears from the brain after death suggested to Avery, Kerr and Ghantus that postmortem glycolysis might also be more rapid than had heretofore been supposed. They therefore examined the brain of the cat and of the dog for lactic acid content, using the method of preparing the tissue which yielded the maximum values for phosphocreatine. It was found in average concentrations of 15.3 mg. per hundred grams in cats and 22.3 mg. in dogs. These values fall within the range obtained by investigators for "resting" muscle and blood.

PAGE, New York.

THE GENESIS OF INHIBITION OF THE CARDIAC GANGLION OF LIMULUS BY STIMULI OF INCREASING FREQUENCY. W. E. GARREY and F. P. KNOWLTON, J. Cell. & Comp. Physiol. **5**:415, 1935.

With any appropriate rate of stimulation of the cardiac ganglion of Limulus, the inhibitory effect increases with the increase in the rate of stimulation, and with an appropriate rate of stimulation the inhibitory effect increases with the intensity. Similar phenomena have been described by Forbes (1922) in regard to spinal reflexes of mammals. Independent of the rate or type of stimuli which cause complete inhibition, this state involves the entire length of the ganglionic cord and is not confined to the restricted locus of stimulation. At high temperatures, inhibition, even with high rates of stimulation, was usually only partial and difficult to sustain.

Garrey and Knowlton consider inhibition as definitely an active process in which the automatic rhythmogenic functions are suppressed, in which a reduction in the respiratory metabolism takes place and in which the cells fail to respond to stimulation. There is in these respects a complete parallel to the peripheral inhibition in heart tissue innervated by the vagus nerves. Excitation and inhibition are only phases of a single process, and when inhibition is complete excitation is an impossibility. Inhibition is considered to be due to some reversible physical state induced by the antecedent excitatory process. Since the inhibitory state may be the after-effect of repetitive excitation, it would spread pari passu with the spread of excitation.

CHORNYAK, Philadelphia.

THE DISTURBANCES AFTER LAMINAR THERMO-COAGULATION OF THE MOTOR CEREBRAL CORTEX. J. G. DUSSER DE BARENNE, Brain **57**:517, 1934.

By laminar thermocoagulation it is possible to destroy at will any consecutive layers of the cortex, starting from the surface, leaving the inner layers intact. In a previous communication Dusser de Barenne reported that with this method apparently normal motor reactions can be obtained from the motor cortex on electrical stimulation after destruction of the outer three layers. Evidence was produced indicating that the reactions from the motor cortex are in all probability

elicited by direct electrical excitation of the bodies of the large and giant pyramidal cells of the fourth layer.

In the present communication Dusser de Barenne compares the disturbances following thermocoagulation of the whole thickness of the cortex of the motor arm area with those following destruction by thermocoagulation of only the outer three layers of the cortex in the same area in Macacus rhesus. In the former, the clinical picture is essentially the same as after surgical extirpation of this area: total paralysis of the contralateral arm for a number of days, which gradually subsides until after three to four weeks motor disturbances are no longer detectable. In the latter there were found very mild motor disturbances, consisting of a slight clumsiness in finer movements of the contralateral hand, which disappeared in about six hours. These findings lead to the conclusion that the severe motor symptoms after destruction of the whole thickness of the motor cortex are due to destruction of the inner two layers.

SALL, Philadelphia.

THE VASO-DILATOR ACTION OF ADRENALINE. G. A. CLARK, J. Physiol. **80**:429 (Feb. 28) 1934.

There is much evidence to show that the action of epinephrine varies both qualitatively and quantitatively in different parts of the body. The vasodilatation caused by epinephrine in skeletal muscle is a purely peripheral effect, for it has been observed after all nerves to a limb were cut and also in isolated perfused limbs, but there is no conclusive evidence to show whether epinephrine in small doses can exert on all minute vessels in the body a dilator action which is definitely peripheral.

Clark investigated the action of minute amounts of epinephrine, given intra-arterially, on the flow of blood through skeletal muscle, intestine and skin in the cat. He found that the response of vessels of muscles to a single injection is of a twofold nature, first dilatation and then constriction occurring, although cases are recorded in which only constriction was seen when the smallest dose of epinephrine that would give any response was administered. This response to epinephrine in the vessels of skeletal muscle is not qualitatively altered by any change in body temperature likely to be found under physiologic conditions. Evidence is given of the release of a dilator substance analogous to Cannon's sympathin I, when only inhibitor or dilator sympathetic endings are stimulated by epinephrine, stimulation of constrictor endings being prevented by the administration of ergotoxine.

The smallest effective amount of epinephrine always produces a diminished flow of blood through the intestine and the skin. In the intestine, but not in the skin, this response is reversed by previous injection of ergotoxine.

ALPERS, Philadelphia.

JUVENILE DEMENTIA PARALYTICA. WILLIAM C. MENNINGER, Arch. Path. **19**:316 (March) 1935.

The characteristic macroscopic changes in cases of juvenile dementia paralytica include generalized atrophy, hypoplasia of the brain (frequent), a marked leptomeningitic reaction, hydrocephalus (frequent) and extensive ependymitis granulosa. The cerebellum often shows atrophy. In rare cases there is an associated formation of gummas in the brain. Because of proliferation of neuroglia, both the cerebrum and the cerebellum are usually very firm. The characteristic microscopic observations include generalized round cell infiltration, an extensive proliferation of neuroglia and microglia, an increase in vascularity, with proliferative changes of all the elements of the walls of the vessels, a reduction in the number of nerve cells in the cortex and changes in the nerve fibers. The frequent finding of binucleated Purkinje cells in the cerebellum is characteristic of, though not limited to, this disease.

A case is cited in which sclerosis of the posterior columns and pyramidal tracts in the spinal cord without symptoms indicating these lesions was observed. In

a small percentage of cases spirochetes were demonstrated in the brain, the cortex, the basal ganglia and the cerebellum.

Menninger believes that several features are characteristic of the juvenile form of dementia paralytica. On gross examination, atrophy, leptomeningitis and pachymeningitis, hydrocephalus and more extensive ependymitis granulosa are observed; in the microscopic picture there is a tendency for the degenerative to exceed the inflammatory changes; the neuroglia and microglia show excessive proliferation, and there are numerous binucleated Purkinje cells in the cerebellum.

WINKELMAN, Philadelphia.

HEMICHOREA ASSOCIATED WITH A LESION OF THE CORPUS LUYSII. J. P. MARTIN and N. S. ALCOCK, Brain **57**:504, 1934.

The patient, a man, aged 65, with sclerotic arteries and a blood pressure of 210 systolic and 130 diastolic, suddenly experienced violent jerking movements first of the left leg and then of the left arm. There were no movements of the face. The movements were irregular, involuntary and of large amplitude and involved the entire limb. The patient died eight days after the onset, and study of the brain revealed marked atheroma of the basal arteries and a small recent hemorrhage involving the greater part of the right side of the corpus Luysi, part of the anterior and lateral portions being spared. There was also a minute hemorrhage at a slightly higher level in the right side of the thalamus, which Martin and Alcock reject as having any clinical importance.

Von Santha (1932) claimed that there was a "somatotopical" relationship between lesions of the corpus Luysi and chorea, the anteromedial or oral pole being associated with the face, the middle part with the upper limb and the posterior portion with the lower limb. The findings in the case cited are in accord with Von Santha's suggestion.

Many cases have been reported as instances of hemichorea in which the damage has been ascribed to structures other than the corpus Luysi. Wenderowic (1928) found the corpus Luysi relatively intact and attributed the hemichorea to irritation of the internal capsule. Wilson (1929) attributed his case to atrophy of the postcentral gyrus. Lewandowsky and Stadelman (1912) described a large lesion involving the lateral part of the thalamus and the internal capsule; it extended into Forel's field. Zannoni (1908) and Malan and Civalleri (1921) described lesions in the upper part of the thalamus. Fragnito and Scarpini (1926) described softening in the right side of the corpus striatum. Martin and Alcock conclude that there is very little reliable evidence that focal damage to any structure in the brain other than the corpus Luysi or its emergent fibers results in hemichorea. They also conclude that hemiballism following a lesion of the corpus Luysi does not differ from other types of chorea except in intensity.

SALL, Philadelphia.

CONTRIBUTION TO THE PATHOLOGY OF THE SPINAL DURA MATER (SPINAL HEMATOMA AND SPINAL PACHYMENINGITIS HAEMORRHAGICA INTERNA). ERWIN RUTSHAUSER, Ann. d'anat. path. **12**:51 (Jan.) 1935.

Rutshauser reports three cases of rare hemorrhagic disease of the spinal dura mater. Case 1 was that of an infant who lived only three weeks. Delivery was rapid, with cephalic presentation. The child was dyspneic soon after birth, with marked muscular hypotonia. He was unable to move his limbs, and only ten days after birth did he show rare, feeble movements of his extremities. Before death paraplegia was complete. The child died of bronchopneumonia. Autopsy showed epidural and subdural organizing hematomas extending downward from the level of the fifth cervical vertebra and becoming more marked caudally. The organizing blood was enmeshed in newly formed connective tissue, which was most evident on the dorsal epidural surface but extended even along the anterior surface of the subdural space. The spinal roots were caught and compressed by this resorbing blood and connective tissue. The cord was intact. There were no

demonstrable tears in the meninges. There was no evidence of injury to the vertebral column. The author concludes that an injury at birth was responsible for the hemorrhages, in spite of the absence of other evidence of trauma. The trauma being so minimal, he suggests a constitutional factor to account for the extensive epidural and subdural bleeding.

Case 2 was that of a female infant, who was delivered normally and died at the age of 9 months. On the second day after birth generalized convulsions appeared, which continued to the day of death. Between attacks the fontanels were slightly tense, and the child was unable to hold up its head. Relatives of the baby considered it mentally abnormal. A lumbar puncture, done two and one-half months before admission to the hospital, elicited a clear fluid with no significant changes. At a second puncture, a few days before death, the spinal fluid was bloody. Remissions were observed during the last few weeks. The last six weeks before death the child had fever which occurred after a cutaneous infection. Autopsy showed pachymeningitis haemorrhagica interna on the inner surface of the whole of the intracranial dura mater. These dural changes were present also in the spinal meninges, where they were less marked and hardly present caudally. One of the layers of the cerebral pachymeningitic membrane was infected. Rutshauser notes the rare occurrence of pachymeningitis haemorrhagica interna in children, especially in the spinal dura. The spinal dura is often not examined at autopsy. He comments on the frequency of purulent infection of the pachymeningitic membrane. In this case he considered the complicating infection metastatic from either the furunculosis or a hemorrhagic bronchopneumonia which was observed at necropsy. He reports that in three of twelve cases of pachymeningitis which he has studied such a terminal purulent inflammation was noted. He also warns against one's concluding that such infections are postoperative and urges that routine smears and cultures he made during trephining in cases of this type.

Case 3 was that of a woman, aged 62, who complained of vague backache for a few months before death. The pain suddenly became more intense and radiated down both lower extremities. The pains became increasingly severe, so that she had to go to bed. Within twenty-four hours there developed complete flaccid paraplegia, with absence of all reflexes except the left achilles tendon reflex. A doubtful Babinski sign was present on the right. There was absence of sensibility to touch up to 10 cm. below the knee anteriorly, and posteriorly in the perianal region. A suboccipital puncture showed bloody spinal fluid; injection of iodized poppy-seed oil 40 per cent showed a block from the eighth to the twelfth dorsal segments. Autopsy revealed a decubitus ulcer, stercoraceous ulcers of the transverse colon, thrombosis of the right femoral vein and embolism of the artery supplying the inferior lobe of the right lung. The brain and its meninges showed nothing abnormal. There was slight osteoporosis of the vertebral column. Clotted blood was found in the spinal subdural spaces surrounding the cord. Most of the blood was in the region of the cauda equina, though some blood was present also in the cervical region. There was no blood in the subarachnoid space. The cord was grossly intact. The whole of the spinal dura mater showed pachymeningitis haemorrhagica interna. Three definite layers were present.

Rutshauser emphasizes the difference between a traumatic hematoma and that of the histologic picture of true pachymeningitis haemorrhagica interna. Traumatic hematoma is not a progressive process and generally shows a tendency to resorption . He also insists that pachymeningitis haemorrhagica interna does not have a traumatic etiology. Subdural hematoma is not the same as vascular pachymeningitis haemorrhagica interna.

SAVITSKY, New York.

THE HISTOPATHOLOGY OF TUBERCULOUS MENINGO-ENCEPHALITIS: I. THE MENINGES. LAVASTINE and AMOUR F. LIBER, Encéphale **30**:77, 1935.

Three cases of diffuse tuberculous meningo-encephalitis in adults are reported. The free cells of the leptomeningeal infiltrate are classified as follows: (1) banal

inflammation cells, lymphocytes, epithelioid cells, etc., which are generally arranged in diffuse sheets, not in follicles; (2) polygonal basophilic cells, which are mobilized fibroblasts and become granular cells, and (3) cells derived from the leptomeningeal covering, of which three types are distinguished—(*a*) large cytophages, (*b*) fusiform cells and (*c*) spongy pyriform cells. Transitional forms are found between these three types and between them and the covering cells. The latter are seen in different stages of mobilization and proliferation, both in the subarachnoid spaces and in the arachnoid villi. The epithelioid cells seem to be derived from monocytes. Giant cells, which are very rare, are of two types: (1) the usual foreign body type, associated with epithelioid cells, and (2) cells derived from vascular endothelium, not associated with epithelioid cells. The tubercle bacilli, which are very abundant, are found on the surfaces of the large cytophage cells, apparently without producing any necrosis. Bacilliferous cell masses, composed of fusiform, pyriform and polygonal cells, undergo necrosis without going through the epithelioid or giant cell stages. The interstitial substances of the infiltrate are (1) a fine albuminous coagulum, (2) free connective tissue fibers and rarely (3) fibrin or fibrinoid substances. In one case, the dura presented zones of necrosis, with slight lymphoid infiltration and without bacilli.

LIBER, New York.

A FAMILIAL FORM OF OLIGOPHRENIA WITH ROENTGENOLOGICALLY DEMONSTRABLE AND SYMMETRICAL DEPOSITS OF CALCIUM IN THE BRAIN, PARTICULARLY IN THE BASAL GANGLIA. R. FRITZSCHE, Schweiz. Arch. f. Neurol. u. Psychiat. **35**:1, 1935.

Of a family of seven children born of second cousins, three, a man, aged 29 years, and two women, aged 28 and 20 years, respectively, were mentally deficient and had dysarthria. The brother and younger sister were said to have had convulsive seizures in childhood. The oldest of the three had begun to show some disturbance of gait in early childhood, and movements of his hands became awkward during adolescence. Similar difficulties had been experienced for the first time by the older sister three years previously, and, as in the brother's case, symptoms had progressed. Both patients presented muscular rigidity of extrapyramidal type, with retropulsion but no tremor; there were also a few signs of cerebellar involvement. Save for the dysarthria, however, examination of the younger sister yielded no definite evidence of a lesion of the central nervous system. Extensive calcification of the corpus striatum and adjacent centrum semiovale was demonstrated roentgenologically in all three patients. In the two older patients the dentate nucleus was also involved.

The absence in the younger sister of neurologic signs in the presence of extensive intracranial calcification seemed to argue against the diagnosis of a primary degenerative process. A review of the literature led Fritzsche to conclude that the condition was essentially metabolic and that the calcification was secondary to a deposit of pseudocalcium in the walls of the blood vessels.

DANIELS, Denver.

MICROGLIA AND THE DIFFUSE PERICELLULAR RETICULUM. F. BIANCHINI, Riv. di neurol. **8**:40 (Feb.) 1935.

Bianchini studied the brains of rabbits and of 30 day old cats according to the method of Belloni with the purpose of investigating the participation of the microglia in the formation of the reticulum. He was able to demonstrate at this early stage that the microgliablast sends out processes which fuse with the diffuse pericellular reticulum. He concludes that the microglia participates in the formation of the diffuse pericellular reticulum.

BARRERA, New York.

ANATOMIC AND HISTOLOGIC STUDIES IN CASES OF SCHIZOPHRENIA. F. MEYER, Monatschr. f. Psychiat. u. Neurol. **88**:265 (May) 1934.

Meyer reports the results of pathologic study in five cases of schizophrenia in which the mental illness was acute in onset and relatively short in duration. The patients were women, their ages varying from 25 to 42 years. All died suddenly without symptoms of somatic disease. In all cases necropsy disclosed severe gastro-enterocolitis of a hemorrhagic, infiltrative-productive or atrophic type, with hyperplasia of the mesenteric lymph nodes. The thyroid, adrenal and pituitary glands exhibited proliferation of the interstitial tissues, which was frequently very pronounced. In four cases there was evidence of marked activation of the reticulo-endothelial elements of the liver, spleen, adrenal glands and lymph nodes. Considerable increase of connective tissue was observed in the liver, pancreas and kidneys. Accumulations of round cells were occasionally encountered in the adrenal glands, liver and hypophysis. The pia-arachnoid was thickened and showed fibroblastic proliferation and edematous swelling in some places. Its meshes contained scattered erythrocytes and macrophages. In four cases the cerebral cortex exhibited a severe diffuse loss of nerve cells, with small acellular areas. In one case several vessels of the internal capsule contained emboli composed of gram-positive cocci, and in another accumulations of micrococci were observed in the capillaries of the liver, the splenic sinuses and the bronchi. Tubercle bacilli were not found. The gastro-enterocolitis was not specific of any particular disease or organism, and no opinion as to its etiology is advanced. However, Meyer has not encountered such changes in patients with other psychoses. The proliferation of connective tissue, the activation of the reticulo-endothelial system and the accumulations of round cells were looked on as secondary, that is, as reactions to some toxic influence. It is possible that the changes in the central nervous system were also of toxic origin. Meyer does not consider further conclusions justified, but he is of the opinion that systematic study of all organs of the body in suitable cases of schizophrenia might add greatly to the knowledge of this puzzling disorder.

ROTHSCHILD, Foxborough, Mass.

Psychiatry and Psychopathology

THE DEPRESSION AND MENTAL DISEASE IN NEW YORK STATE. HORATIO M. POLLOCK, Am. J. Psychiat. **91**:763 (Jan.) 1935.

The ten year period beginning in 1924 may be divided into two five year areas: (1) an era of prosperity from 1924 to 1929 and (2) an era of depression from 1929 to 1934. Pollock examines the statistics pertaining to admissions to hospitals for patients with mental disease during these two periods to determine what effect the depression has had on the incidence of certifiable mental disease. During the prosperity quinquennium the average annual increase in the population in the state hospitals was 1,600; during the depression half of the decade the corresponding average was 2,500. The rate of patients admitted for the first time per hundred thousand of general population rose from 68 in 1924 to 85 in 1933. Private institutions are included in the census, so that the shift of large numbers of patients from private to state hospitals would not affect these figures.

Examining the statistics for each psychosis separately, Pollock finds little significant change in the number of cases of dementia paralytica, alcoholic psychosis or senile dementia. The rate of admission for patients with manic-depressive psychosis increased slowly from 7 per hundred thousand at the beginning of the decade to 8.1 in 1933. The proportion of patients with manic-depressive psychoses who were admitted for the first time, however, remained substantially unchanged. The rate of admission for patients with dementia praecox rose from 18 per hundred thousand in 1924 to 22 in 1933. The most remarkable change occurred in the rate of admission for persons with cerebral arteriosclerosis. At the beginning of the decade it was 7 per hundred thousand; at the end of the survey, in 1933, it rose to almost 16 per hundred thousand. Pollock concludes that the economic crisis is a precipitating factor of importance in all of the psychotic groups.

DAVIDSON, Newark N. J.

THE SOMATO-PSYCHE IN PSYCHIATRY AND SOCIAL PSYCHOLOGY. PAUL SCHILDER, J. Abnorm. & Social Psychol. **29**:314 (Oct.-Dec.) 1934.

Many psychologists think that much is known about one's own body but little about oneself. In the course of one's life knowledge about one's body slowly increases. According to Preyer, the child at first has the same attitude toward its body as toward other objects. It follows the movements of its arms and legs with its eyes in the same way as it follows a candle-light. It bites its fingers, arms and toes till it cries with pain. As the state of consciousness changes the body image fluctuates. Often just before falling asleep one receives the sensation that the body is changing its proportions. It becomes too large or too small. It may become flat or the legs may disappear. These variations in body sensation are also dependent on the emotional life. The openings of the body have psychologically and physiologically a greater importance than most of the other parts of the body and are usually invested with particular libidinous interest. If one could but mark in a picture of a body the zones which are outstanding in the body image of a particular personality, one would find the emotional tendencies and strivings of that particular person. Since the emotions and the accentuation of particular portions of the body are interrelated, it follows that every disturbance in the emotional life will immediately react on the body image. Unity of the body image is disrupted when libido is too unequally distributed over the body, and to accede to the libidinal demands of the abnormal erogenous zones may provoke a neurosis. If, however, they are admitted into consciousness and expression given to them a perversion may be the result.

Every organ which has been loved too much is in danger of becoming the seat of hypochondriacal sensations, as in the case of opera singers who have symptoms in the mouth and throat. The patient who had felt that her hand was the most beautiful part of her body dreamed that she would meet with an accident and injure the hand. It was not unnatural, then, that she should have suffered an unimportant accident which led to two superficial scars on her thumb, for an organ invested with too much libido exposes itself to traumatism and reacts to it with hypochondriacal sensations. This young lady after the accident felt incapacitated, unable to work, dejected and depressed. Furthermore, disappointment concerning one part of the body may provoke feelings of dissatisfaction with the body as a whole or even feelings of unreality or depersonalization.

WISE, Howard, R. I.

AN EXPERIMENTAL STUDY OF STEREOTYPES. M. SHERIF, J. Abnorm. & Social Psychol. **29**:371 (Jan.-March) 1935.

To prove experimentally that the prestige of a person determines with great bias one's evaluations of his actions and his productions and that preconceptions and prejudices influence to a large extent emotional responses, the following experiment was conducted: Groups of male and female students in two American and one foreign institution for learning were requested to designate the order of their preference for a list of sixteen authors whose names were supplied them, arranged alphabetically. One month later the same subjects were given sixteen short passages of three or four lines, the literary value and the taste for which they were asked to determine relatively. No subject suspected the deception, which was that all the passages were taken from the works of one author, who was not among the names included in the original list. One short passage from Robert Louis Stevenson's works was assigned at random to each of the previously selected authors. The thirty-three Harvard students (who could honestly declare that they had made no special effort to overcome the influence of the authors' names) designated as superior 45 per cent of the passages which were associated with the names of authors for whom they had already shown preference. A group of Radcliffe girls were influenced to such an extent that 63 per cent of the passages were admired when they were associated with favorite writers. A group of

students working in a psychologic laboratory in Ankara, Turkey, correlated 47 per cent of choices with the previously expressed opinions. This indicates clearly the influence of prestige (stereotype) in the literary field. It is therefore reasonable to presume that a similar influence prevails in economic, political, religious and theoretical fields.

WISE, Howard, R. I.

BODY SYMBOLIZATION AND THE DEVELOPMENT OF LANGUAGE. LAWRENCE S. KUBIE, Psychoanalyt. Quart. **3**:430 (July) 1934.

Since during infancy and childhood cravings arise in body tensions, it is inevitable that the child's thought world should begin with his body and that his first concepts must deal with the parts, the products, the needs and the feelings of the body. In order to understand the growth of language one must observe closely what the child wants, what parts of the body become involved in the process of wanting and ultimately how he learns to speak and think of the different parts of the body and of the desires and feelings associated with them.

Since the child's world begins inevitably with his body, since the force which instigates the child to expand his knowledge is always the pressure of bodily desires and since every new fact of experience which enters into psychic life can make its entrance only by relating itself to that which is already present, it follows that every new fact perceived by the child must somehow relate itself to bodily things. Thus, in the examples cited by the author, a little boy referred to his feces as the Chrysler building, and a little girl spoke of her father's genitals as the mouse. A little girl playing with her father suddenly pressed her genitals against his face and said, "Come on, let us play you're a snake." Another child insisted on pinning a safety-pin on the front of her shirt as a substitute for a penis. While playing with a mechanical toy, a boy unscrewed the bolts and took it apart. When scolded, he became excited and said that if he could find a certain hole there would be a baby in it. The same boy offered to draw on the board a wreck of engines at night; when the teacher came to the board she found that the child had drawn a man and a woman. Many such examples are cited by the author. All these demonstrate the occurrence of indirect representation of those parts of the body which are connected with emotion and vegetative functions early in the development of the child.

KESANIN, Chicago.

CHILD ANALYSIS AND THE MOTHER. DOROTHY T. BURLINGHAM, Psychoanalyt. Quart. **4**:69, 1935.

The analysis of a child presents certain difficulties not encountered in the analysis of an adult. These are: (1) the child's relative inability to express himself in words and (2) the emotional relation of the child to the analyst, which is complicated by his natural attachment to his parents and which forces the analyst to keep the latter in a favorable attitude toward the analysis. The latter is the problem dealt with in this paper. Proper handling of this situation is of great importance in preventing premature termination of the analysis. Burlingham deals with this problem in relation to mothers, because the analyst deals with them almost exclusively. Whether the mother is ignorant of analysis or whether she knows something about it, difficulties arise because the analyst's suggestions at certain points in the analysis often conflict with the mother's unconscious needs. After enumerating the many minor difficulties which arise in analysis owing to the mother's attitudes to life and to the child, the author points out that analysts have tried to meet this situation in three ways: (1) by ignoring the mother even to the extent of leaving out all the child's early life and extra-analytic reactions; (2) by removing the child from the home during the course of the analysis, and (3) by including the parents in the treatment, showing them step by step what is being attempted, thus giving them an insight into the child's troubles so that they can change outer and inner activities which tend to increase the child's neurosis.

The first method leaves the child out of touch with reality except in the analytic hour. After such an analysis, although he may be aware of his conscious and unconscious reasons for all his actions in his early life, he seems like a ship at sea. He cannot use his newly acquired understanding of himself to adjust to reality. His world is changed only so far as his symptoms interfered with his ability to meet it. His environment, which was conducive to the formation of the neurosis, has not changed, although he can meet it less neurotically. He still has the same situations to fight.

The second method has some advantages. The child's parents may be so neurotic that an analysis at home is impossible. It is easier for the analyst to understand the child's neurosis in a less complicated environment. After the analysis, when he is returned home to the situation where his neurosis started, he often cannot adjust himself in that situation and perhaps begs to be sent away again.

The third method is the most difficult but perhaps the best, because the analyst must carry the parent's difficulties as well. The mother is bound to develop jealous criticism and hurt feelings, because the analyst has really come between her and her child and she feels that she must protect her rights. There are ways of meeting this situation. The analyst must show that he is interested not only in the child but in the mother as well. The latter must be encouraged in the treatment by bringing to the analyst any information that she feels is important and by observing and recording the child's behavior between the analytic hours. If she feels that she is taking part in a piece of research, her interest becomes awakened. She begins to bring in material about herself, making comparisons between herself and the child.

The analyst also can count on help from the mother's feeling of guilt concerning her rearing of the child. She feels that she could have done more for him and looks to the analyst for help in undoing her mistakes. The analyst must initiate the mother into each step in the treatment so that she will not be shocked or unprepared and so that she can help the child adjust to his new freedom.

PEARSON, Philadelphia.

DEVELOPMENTAL STUDY OF THE OBSESSIONAL NEUROSIS. EDWARD GLOVER, Internat. J. Psycho-Analysis **16**:131 (April) 1935.

In earlier studies of the neuroses the kernel of the problem revolved around the Oedipus situation, with certain fixation levels responsible for the different types. Thus, the obsessional neuroses owe their origin to the common factor of castration anxiety, with specific clinical symptoms caused partly by constitutional factors and partly by precocious ego development. There are, in addition, special experiences of anal-sadistic ambivalence, diffusion of the instinct of frustration and a marked quantity of regression. It was found later that the same etiologic factors were present in other neuroses. Glover stresses the necessity of a search for specific factors and points out that these must be sought in two directions: (1) in combinations of endopsychic factors and (2) in environmental stimuli. In discussing the various methods of study he attempts to discover what developmental phases are reflected or caricatured by the symptom construction. The aim of the obsessional neurosis is to prevent the emergence of painful affect; hence the various rituals and ceremonies. Regression, which one observes in the obsessional neurosis, is largely a strategic withdrawal to earlier psychic levels. By this withdrawal the subject secures the mental rites, privileges and methods of defense peculiar to those earlier levels which give him an opportunity to tackle life with reenforced, though antiquated, methods. Glover believes that the obsessional states date back to early childhood, when the infant is trying to find some way of dealing with overwhelming affects.

KASANIN, Chicago.

THE USE OF THE TERM "ACTIVE" IN THE DEFINITION OF MASCULINITY. IMRE HERMANN, Internat. J. Psycho-Analysis **16**:219 (April) 1935.

Hermann objects to the equation of the word "masculinity" with "activity." It has even been suggested that the only libido is male libido. These statements are erroneous for the following reasons: Libido is a quantitatively variable energy of the sexual instincts, and it is neither male nor female exclusively. In using the terms "active" and "passive" there are several possibilities, some of which are: Activity is usually taken to denote a special mode of activity in the male, while the fact that there is another kind of activity in the female, such as expresses itself in coquetry and seduction, is usually ignored. The whole conception of woman's passivity is not a true conception but is in the nature of an "ideal." At certain periods of civilization the code of sexual morality refused to recognize activity in the sexual life of women. There was thus a deliberate attempt to make activity and masculinity synonymous. It is neurotic anxiety which caused many men to insist on passivity in women, especially in the sexual act. People are led astray by the erroneous conclusion that "active" is synonymous with "masculine" because in the sexual act the man penetrates whereas the woman passively receives. This is, however, a mere juggling of words, for the man cannot penetrate a woman's body unless she actively makes herself accessible to him. There is no basis for the antithesis of active penetration versus passive reception; such a notion eliminates the psychic factor and substitutes machines for living beings. What actually occurs is the active desire on the part of the male to penetrate and the active desire on the part of the woman to receive.

From these facts certain conclusions can be drawn: Biologically there is good evidence for the activity of the female. This can be seen not only in human beings, but also in the apes, among whom the female is conspicuously active in the sense of presenting herself. In analytic situations the tendency to seduce in women is well known and important. There is just as much aggression in women as there is in men. Even though the man may commit the aggressive act, the woman may be the one responsible for it. According to some definitions, activity denotes giving and passivity receiving; this is not true, because while the man gives his penis to the woman he receives her body in his embrace and she, receiving his penis, his semen and his body, gives hers. This discussion has one important bearing on analysis. One cannot analyze a woman successfully if one claims that if she is active in her sex life she is necessarily masculine.

KASANIN, Chicago.

PERSEVERATION AND PERSONALITY: SOME EXPERIMENTS AND A HYPOTHESIS. RAYMOND B. CATTELL, J. Ment. Sc. **81**:151 (Jan.) 1935.

Perseveration is defined as the lag, inertia or persistence of a mental process. It has been especially studied by Spearman, who, with students, has developed a special test for measuring this function. In the course of two and one-half years, fifty-two persons, twenty-three men and twenty-nine women were tested. Cattell finds that perseveration cannot be correlated with extraversion-intraversion but can be correlated with certain personality traits. The "low perseverator" is masterful, is not sensitive and is not afraid to hurt the feelings of others. He is enterprising, individualistic and erratic and also irritable, assertive and domineering. He has definite tastes and is practical, sure of himself and fond of audiences, but he does not exhaust himself in the service of a cause. The personality balance is put before anything else. The "high perseverator" seems to be resigned and finds expression in diffuse ways. He shows lack of initiative and is quiet, withdrawn, helpless and sensitive of other people. He is emotional, although he does not show his feelings. He is absent-minded and is dreamy and contemplative. He works well alone, does not care for public opinion, shows poor taste, is overserious and lacks a sense of humor. He shows deeper sexual coloring, with the whole personality being more obviously masculine or feminine. The low perseverator possesses a certain childlike freshness and gusto. One might summarize the difference by

saying that a low perseverator is American in outlook; the high perseverator, French. Cattell postulates that perseveration is essentially an indication of nervous debility, indicating nervous exhaustion. High perseveration is also an indication of deep conflict, discouragement and inhibition induced early in life. He suggests that the low perseverator probably has had a healthy atmosphere in childhood, with strict and objective discipline, and for this reason is less likely to suffer from emotional conflict and frustration than the child who lived with emotional turmoil in the home. The characteristic failings of the low perseverator arise from inadequate inhibition and thoughtfulness; those of the high perseverator, from too profound conflict and discouragement.

KASANIN, Chicago.

PHYSICAL SYMPTOMS IN ACUTE CONFUSIONAL INSANITY. L. C. BRUCE, J. Ment. Sc. **81**:282 (April) 1935.

Acute confusional psychoses are a group of diseases which occur during adolescence and middle age; they are not common during the climacteric or during old age. There is a prodromal period of mild confusion, incapacity for connected thought and sleeplessness. This is followed, often suddenly, by complete lack of knowledge of time and place, with vivid and often terrifying hallucinations of hearing and sight, great motor restlessness and rapid action of the heart. Delirium, more or less severe, is always present in the first attacks. The patient looks ill; there are sordes on the teeth and lips, the tongue is dry, foul and cracked, and the habits are untidy. With nursing and care, 90 per cent of the patients recover. First attacks almost always end in recovery, though they may last for two or three years.

In most of the cases there are no disturbances of temperature. In a small group fever is present; with a decrease in the temperature the mental symptoms disappear. In the afebrile group, which comprises most of the patients, there is marked improvement, with recovery, if an intercurrent disease supervenes accompanied by increased temperature. In 1908 Bruce drew attention to the fact that there is marked leukocytosis in the acute stage of the disease, which serves as a defense of the organism. Since there is eosinophilia in such cases toward the end of the attack, this may be considered a sign of recovery. Bruce has never seen recovery without leukocytosis. It does not follow, however, that because there is no leukocytosis there will be no recovery. There was albumin in the urine in 60 per cent of the cases and bacteria, white cells and false tube casts were noted in 40 per cent. The symptoms of irritation last only a few days. Positive cutaneous reactions to streptococcus filtrate were found in fourteen of the twenty cases. There is a definite hypoglycemia, and sugar tolerance tests show that the blood sugar content drops below normal after two hours. Bruce again emphasizes that in some conditions labeled "mental" there is a widespread departure from health which must be explained in medical rather than in psychologic terms.

KASANIN, Chicago.

STERILITY AND PSYCHONEUROSES FOLLOWING LUMBAR SYMPATHECTOMY. ARTHUR F. HURST, Lancet **1**:805 (April 6) 1935.

Hurst reports two cases in which sympathectomy in the lumbar region caused sterility, which was followed by psychoneurosis. In 1931 Learmonth pointed out that when the presacral nerve is stimulated in men a cloud of seminal fluid and prostatic secretion is poured into the prostatic urethra as a result of contraction of the seminal vesicles, ejaculatory ducts and muscular septums of the prostatic gland. The following year Learmonth added that patients must obviously be warned that operation will be followed by sterility, although not by impotence. Neurectomy of the presacral nerve does not appear to affect the sexual function in women, according to Learmonth. Hurst reports two cases, one of a man aged 47 and the other of a man aged 45, in which sympathectomy was performed in the lumbar region. Although each could perform the sexual act, each seemed greatly worried because the act terminated without the occurrence of an emission. In both patients a psychoneurosis developed.

WATTS, Washington, D. C.

THE RÔLE OF EXOGENOUS AND ENDOGENOUS FACTORS IN THE PRODUCTION OF SYMPTOMATIC PSYCHOSES. I. SOMOGYI and A. Z. RÁTH, Monatschr. f. Psychiat. u. Neurol. **88**:173 (March) 1934.

Somogyi and Ráth studied 200 cases of symptomatic and toxic psychoses caused by infections, trauma, encephalopathic processes, intoxication produced by alcohol and morphine and autointoxication, such as circulatory insufficiency, disease of the kidneys, diabetic coma and cachexia due to carcinoma. One hundred and five patients showed a purely exogenous type of mental reaction. In 90 per cent of these patients the illness developed acutely or caused massive and generalized damage to the central nervous system. Ninety-five patients presented clinical pictures which were colored by symptoms belonging to endogenous types of mental reaction, such as manic-depressive psychosis and schizophrenia. The exogenous agents were almost always insidious and chronic in action, toxic and encephalitic processes being encountered with greatest frequency. Indications of constitutional predisposition to endogenous mental disorders were observed in 75 per cent of these patients. Less marked evidence of similar constitutional tendencies was noted in 24 of the patients who presented a purely exogenous type of mental reaction. In 12 patients mental symptoms of an endogenous type occupied the foreground of the clinical picture. Somogyi and Ráth found that when the onset of an exogenous psychosis was acute and the course stormy, either recovery or death occurred. Even with the slowly developing, chronic disorders, endogenous mental features persisted in only 10 per cent of the cases. It is probable that an exogenous psychosis characterized by clouding of consciousness, delirium or amentia-like symptoms will develop if the exogenous agent acts suddenly and exerts its effects on the whole brain. Less powerful noxious agents may produce a similar reaction if they are able to penetrate the meningeal, vascular and mesodermal barriers with ease. In cases of this type one may say that a constitutional weakness of the mesodermal components of the nervous system is an important etiologic factor. Somogyi and Ráth are of the opinion that endogenous mental disorders are based on hereditarily conditioned elective degeneration of ectodermal nervous elements. If there is a constitutional weakness of ectodermal elements, symptoms belonging to an endogenous type of mental reaction may be elicited by exogenous disease, and if this weakness is pronounced an endogenous psychosis may persist indefinitely, even though the exogenous disease has disappeared. Apparently endogenous factors play no rôle in the immediate production of symptomatic and toxic psychoses.

ROTHSCHILD, Foxborough, Mass.

Meninges and Blood Vessels

MENINGOCOCCIC AND NONMENINGOCOCCIC MENINGITIS IN THE NEW-BORN AND IN YOUNG INFANTS. J. ATWELL RAVID, Am. J. Dis. Child. **49**:1282 (May) 1935.

Ravid calls attention to the fact that because of atypical and varied types of manifestations of meningitis in the new-born and in infants the diagnosis is frequently missed, and the condition is mistaken for gastro-enteritis, congenital debility, marasmus and tetany. Ravid reports a series of cases of both the meningococcic and the nonmeningococcic type, in which the neurologic symptoms were relatively few and symptoms referable to the gastro-intestinal and the respiratory tracts predominated. He includes a statistical study of cases of meningitis in children which shows that only 2.5 per cent of the cases of meningococcic meningitis and 4.1 per cent of the cases of nonmeningococcic meningitis occur in infants 3 months of age or younger. He emphasizes that the clinical manifestations may be different from those in older children. In the absence of definite signs of involvement of the central nervous system or of evidence of meningeal irritation, an irregular fever with gastro-intestinal disturbances of any sort which occur without demonstrable cause and which do not respond readily to treatment should

lead one to suspect the presence of meningitis. Hyperesthesia, irritability, somnolence, increased cranial pressure, distention of the veins of the neck, incessant crying and a dissociation between the pulse and the respiratory rate and the temperature are considered to be significant.

The pathogenesis of the meningococcic type is considered to be essentially the same as that in older children. Of the nonmeningococcic variety, streptococcic, pneumococcic and tuberculous involvement are considered to be essentially the same. Infection with Bacillus coli and related organisms appears in infants during the first three or four months of life. It is rarely seen in older children.

The prognosis in all forms of meningitis in young children, especially during the first year, is extremely poor, the mortality rate for the nonmeningococcic variety being almost 100 per cent and for meningococcic meningitis, about 48 per cent. It is believed that this high mortality rate could be considerably lowered if the diagnosis could be made sooner and conservative antimeningococcic treatment instituted. The author is not in favor of the indiscriminate use of the ventricular and cisternal routes for the removal of fluid and the introduction of vaccine and serums.

WAGGONER, Ann Arbor, Mich.

EFFECT OF TISSUE EXTRACTS ON MUSCLE PAINS OF ISCHEMIC ORIGIN (INTERMITTENT CLAUDICATION). NELSON W. BARKER, GEORGE E. BROWN and GRACE M. ROTH, Am. J. M. Sc. **189**:36, 1935.

Barker, Brown and Roth have studied the effects of pancreatic tissue extract, of skeletal muscle extract and of adenosin on intermittent claudication. The cutaneous temperature of the digits was measured in a room at controlled temperature to determine whether significant vasodilatation occurred. In order to evaluate the effect of the various tissue extracts a standard test for claudication was devised. After a rest of one-half hour the patient walks on a level floor at a rate of 120 steps per minute until sufficient distress occurs to cause him to stop. The time elapsed from the beginning of the walk until cessation of it is designated as the "claudication time." Sixteen patients with occlusive arterial disease were tested repeatedly on various days in the same environmental temperature and showed an average variation of only 10 per cent from their claudication time. The tissue extract was injected into the triceps muscle of the arm.

Definite lengthening of the time necessary to produce intermittent claudication during a standard claudication test was noted in 92 per cent of a series of fifty-five cases of thrombo-angiitis obliterans and arteriosclerosis obliterans after intramuscular injections of pancreatic tissue extract. Similar effects were noted in all of a series of eight cases of thrombo-angiitis obliterans after intramuscular injection of an extract of skeletal muscle. In only one of five patients with arteriosclerosis obliterans was an increase in claudication time noted after the muscle extract had been given intramuscularly. In 75 per cent of a series of eight cases of intermittent claudication, in which the patients received the skeletal muscle extract orally, an approximately equal but more transient effect was noted. Definite but less striking increases in claudication time were noted in four cases in which patients received muscle adenosin phosphoric acid intramuscularly and in four cases in which patients received adenosin intramuscularly.

No correlation was found between the cutaneous temperatures and the claudication time. In the experience of the authors, definite vasodilatation does not significantly affect intermittent claudication. They have also observed that tissue extracts have little or no effect on pretrophic pain or on pain which results from the ulceration and gangrene which occur in occlusive arterial disease. They conclude that the lengthening of the claudication time following the administration of tissue juices is the result not of vasodilatation but of some direct action on the contracting ischemic muscles.

WATTS, Washington, D. C.

POSTERIOR INFERIOR CEREBELLAR THROMBOSIS WITH UNUSUAL FEATURES. ARTHUR J. HALL and ELIZABETH COWPER EAVES, Lancet **2**:975 (Nov. 3) 1934.

Hall and Eaves state that occlusion of a posterior cerebellar artery gives rise to a well defined group of symptoms. In a typical case there are sudden vertigo, inability to swallow and more or less sensory loss, usually unilateral in distribution and of a dissociated kind. While the diagnosis was easily made in the case reported, the picture differed from those hitherto recorded. Instead of the unilateral sensory loss being of the dissociated type, all forms of superficial sensation were involved over the whole of the affected area. Autopsy revealed that the only lesion was such as is known to follow occlusion of the posterior inferior cerebellar artery.

The area of sensory loss in the case reported extended over the whole of the right side as high as the lower part of the forehead, including loss of tactile sensation as well as of those of temperature and pain. Posture sense was intact and deep pain sensations persisted. There was slight ataxia of the right leg but none of the right arm. Ataxia was absent on the homolateral side. An area of degeneration corresponding to the distribution of the left posterior inferior cerebellar artery was consistent with occlusion of that vessel. It was smaller than usual.

Hall and Eaves suggest that in this patient tactile impulses from the opposite side traveled through the medulla either with or closely adjacent to those of pain and temperature.

WATTS, Washington, D. C.

TRANSITORY AND CURABLE TUBERCULOUS MENINGITIS AND MENINGEAL BACILLOSIS. PAISSEAU and LAQUERRIÈRE, Ann. de méd. **37**:205 (Feb.) 1935.

The cerebrospinal fluid from a number of patients who were suspected of having tuberculous meningitis was inoculated into guinea-pigs and cultured in the medium devised by Loewenstein. It could be demonstrated that some patients with acute leptomeningitis who survived had acute, transitory and curable types of tuberculous meningitis. Paisseau and Laquerrière discuss the question whether the very small number of tubercle bacilli which could be demonstrated in cultures of material from such patients with the method mentioned indicated that the tuberculous "ultravirus" produced the meningitis or whether one was dealing with an attenuated form of tubercle bacilli. In a number of cases of pulmonary tuberculosis tubercle bacilli could be demonstrated in the cerebrospinal fluid, though neither clinical observation nor laboratory tests had shown meningitis. It is possible either that one is dealing here with attenuated forms or that the meningeal bacillosis preceded the actual inflammatory reaction.

WEIL, Chicago.

THE HISTOPATHOLOGY OF TUBERCULOUS MENINGO-ENCEPHALITIS: II. THE NERVE PARENCHYMA. LAIGNEL-LAVASTINE and AMOUR F. LIBER, Encéphale **30**: 171, 1935.

Diffuse and circumscribed lesions were found mostly beneath the meninges and the ventricles. The neuroglia and the microglia presented proliferative and degenerative changes. A peculiar type of microglial reaction was transformation into forms resembling epithelioid cells. The neuroglia cells sometimes formed proliferative nodules. The ependyma presented hyperplastic foci, either pure or infiltrated with leukocytes and microglia cells, and zones of desquamation. The cells infiltrating the sheaths of the blood vessels were of the same type as those in the neighboring region of the meninges. They seemed not to be directly hematogenous but rather to invade the parenchyma from the meninges. In one case the vascular sheaths contained peculiar basophilic bodies and black pigment. Nodules of vascular origin did not present a follicular structure. The necrotic center was invaded by reticular fibers. The walls of these nodules contained tubercle bacilli and seemed to be zones of extension. The stroma of the choroid plexus was infiltrated with lymphocytes and plasmocytes. Bacilli were found only in the meningovascular infiltrates, not in the neuroglia, microglia or ependymal formations or in the choroid plexus. The spinal nerve roots contained diffuse

infiltrates and atypical nodules, which were rich in tubercle bacilli. From 5 to 10 per cent of the nerve fibers were degenerated. The lesions of the ganglion cells of the nerve centers were of diffuse and haphazard topography. The white matter was unaffected, save for small lacunae of disintegration about infiltrated vessels. The spinal ganglia were only slightly altered. LIBER, New York.

CEREBELLOPONTILE SYNDROME FROM REPEATED CURABLE MENINGEAL HEMORRHAGE IN AN ELDERLY MAN WITH HYPERTENSION. HENRI ROGER, Rev. d'oto-neuro-opht. **12**:582 (Sept.-Oct.) 1934.

Few observations of similar cases have been published. The patient, a man aged 73, with arterial hypertension, experienced a sudden occipital headache during coitus accompanied by nausea, vomiting and vertigo. The arterial tension was 20 systolic and 11 diastolic (Vaquez); there was azotemia, and the urine was free from albumin. The headache was severe and was localized in the right occipital region, with radiations in the interscapular and sacrolumbar regions. There were stiff neck, positive Kernig and Lasègue signs, a pulse rate of 70 and a temperature of 37.4 C. (99.3 F.) Lumbar puncture revealed bloody cerebrospinal fluid; compression of the right jugular vein increased the tension of the fluid to 25, which declined to 10 after the withdrawal of 10 cc. of fluid. Another attack occurred on the following day and one two weeks later; a third attack, one day afterward, was accompanied by pain in the right ear and the right side of the face, facial paralysis on the right side, complete deafness of the right ear, vertigo and nystagmus, chill, sweats and a temperature of 39.6 C. (103.3 F.). Transfusion of 100 cc. of blood was given. Recovery slowly occurred, but three months later paresis of the fifth, seventh and eighth nerves was still present. It is probable that at the time of the first hemorrhage adhesions formed which prevented the ultimate diffusion of the blood to the opposite side and to the convexity. The recurrences resulted in spite of measures directed toward lowering the hypertension and increasing the coagulability of the blood. No more bleeding occurred after the transfusion, but it is difficult to estimate its efficacy.

DENNIS, San Diego, Calif.

SPASM OF RETINAL ARTERIES IN FUNCTIONAL AMAUROSIS RESULTING FROM SUGGESTION. G. ROASENDA, Riv. di pat. nerv. **45**:59 (Jan.-Feb.) 1935.

Roasenda reports the case of a patient suffering from hysteria in which suggestion by the physician resulted in transitory functional amaurosis. The interest of the case lies in the fact that while the physician suggested to the patient the development of the functional amaurosis he was examining the fundus and noted a constriction of the retinal vessels simultaneous with the development of the amaurosis. The blood vessels always resumed a normal caliber as vision returned in the amaurotic eye.

FERRARO, New York.

Diseases of the Brain

JUVENILE PARETIC NEUROSYPHILIS STUDIES: PHYSICAL COMPLICATIONS, STIGMAS, AND ENDOCRINOPATHIES. WILLIAM C. MENNINGER, Am. J. Syph. & Neurol. **19**:88 (Jan.) 1935.

In his series of over 600 cases of juvenile dementia paralytica Menninger finds that 86 per cent of the patients showed one or more of the syphilitic stigmas. The specific stigmas and their frequency were: Hutchinson's teeth, 24 per cent; saddle nose, 10 per cent; choroiditis, 5 per cent; interstitial keratitis, 8 per cent; frontal bosses, 11 per cent; high arched palate, 6 per cent; facial asymmetry, 13 per cent; rhagades, 6 per cent, and a mixed group including osteitis, bowed tibia, hydrocele, etc., 21 per cent. Poorly defined disturbances of the endocrine system are frequently associated with juvenile dementia paralytica and usually take the form of genital hypoplasia or body infantilism. Hypoplasia of the genitalia was found in

33 per cent of the males, while amenorrhea was reported in 25 per cent of the adolescent and adult females. Disturbances of the thyroid gland were found only infrequently and seemed to play no rôle in the development of body infantilism in these cases.

DAVIDSON, Newark, N. J.

ASSOCIATION OF OPTIC NEURITIS, FACIAL PARALYSIS AND FACIAL HEMIATROPHY. E. A. SHUMWAY, Arch. Ophth. **13**:8 (Jan.) 1935.

In 1904 Shumway reported a case of optic neuritis with facial paralysis. At the time the patient was 19 years of age; she complained only of blurred vision, vision being 6/15 in the right eye and 6/30 in the left eye. She was first seen on Dec. 8, 1903. In November 1902 paralysis developed on the right side of the face, which seemed to occur after exposure to a draft. This was preceded and accompanied by severe pain in the lower jaw and teeth and in front of the ear on the same side. The fundi showed bilateral atrophy of the optic nerve. The nerve heads were covered with a delicate white tissue which could be traced in the form of white lines along the central vessels of the retina, though they were somewhat fuller at a distance from it. The fields of vision were slightly contracted but showed no central scotomas. There was definite impairment in the light sense according to the photometric tests of de Wecker and Masselon. In addition, the face showed slight flattening on the right side, with decided enophthalmos. At that time only seven other similar cases had been reported in the literature.

The subsequent history in this case seemed to warrant again calling attention to the subject, particularly as to the etiology, and more because of later developments in the views of neurologists and physiologists as to the functions of the facial nerve.

In 1909 the patient had paralysis of the oculomotor nerve. In 1912 she had a recurrence of facial paralysis. In 1919 she had a third recurrence, this time on the left side. Six months later the right side was again involved. At that time the attending ophthalmologist stated that the third and sixth nerves on the right side also showed involvement. In 1919 she had a large abscess removed from the left superior central incisor and a second from the left lower molar. In 1920, while under examination in the author's office, she showed weakness of the right side of the face and twitching of the eyelids on both sides. Touch and temperature sensations were equal on the two sides of the face. Smell was wholly absent, and there was only a little sense of taste on the anterior part of the tongue. Both optic nerves showed complete atrophy, with blurring of the margins of the disk from an old neuritis; the arteries were narrowed, and the dilated veins were clustered like a bunch of earthworms on the nerve heads. The patient was without perception of light.

In reviewing the case from the standpoint of possible etiology, it was discovered that the teeth, which were abscessed, had been filled six years before the onset of the unusual facial paralysis, "after killing the nerves of the teeth." The diagnosis in the case was polyneuritis of the cranial nerves. The author thought that the condition was due to the dental infection. The anatomic complexity of the seventh nerve could be the basis for the many different pathologic changes which appeared.

The studies of Hunt of herpes of the ear, facial paralysis and disturbances of the auditory nerve in 1907 and 1910, which symptoms are now accepted generally as the Hunt syndrome, have further clarified the views of neurologists as to the functions of the seventh nerve (Aitken and Brain). In the present instance it may be accepted that the facial paralysis was due to facial neuritis and that the atrophy of the face was not a true hemiatrophy (which usually occurs in early life) and was due to inflammation of the fifth nerve. The third, and possibly also the fourth and sixth nerves, were likewise involved. As to the disturbance of smell, this may have been due to involvement of the facial nerve, either by interference with the dilatation of the nasal orifice from weakness of the levator nasi or, more likely, by defective distribution of tears in consequence of paralysis of winking

and of the muscle of Horner, which leaves the corresponding side of the nasal cavity drier than normal. As both facial nerves were affected at different times, entire loss of smell may be accounted for in this way. The loss of taste may also be assumed to be due to disease of the facial nerve, by involvement of the fibers constituting the chorda tympani branch, which come from the glossopharyngeal nucleus, without the necessity of considering involvement of the glossopharyngeal nerve itself, especially in view of the absence of disturbance of the soft palate.

SPAETH, Philadelphia.

OTOGENOUS ABSCESS OF THE PARIETAL LOBE. CYRIL B. COURVILLE and J. M. NIELSEN, Arch. Surg. **30**:930 (June) 1935.

The unusual occurrence of abscess of the parietal lobe secondary to otitis media merits the study of a series of six cases. These cases present nothing unusual from the anatomic or the clinical standpoint. The occurrence of abscess of the parietal lobe secondary to otogenic subdural abscess, to osteomyelitis of the parietal bone or to otitic abscess of the frontal or temporal lobes is believed to be rare. It is most probable that the infection is transmitted to the parietal lobe by way of the venous pathways, as suggested by the frequent association of thrombosis of the lateral sinus and associated venous channels. This may occur with or without gross occlusion of the adjacent veins.

SPERLING, Philadelphia.

MENTAL CHANGES ASSOCIATED WITH PERNICIOUS ANEMIA. C. W. OSGOOD, J. A. M. A. **104**:2155 (June 15) 1935.

Osgood gives the following arguments against pernicious anemia's being the primary cause of an associated psychosis: 1. There is very often a family history or personal past history of mental disease. 2. The psychoses present no characteristics that clearly distinguish them from endogenous depressions or other well recognized mental disorders. 3. Mental improvement, when present, does not parallel the physical improvement. 4. Necropsy shows no consistent relation between the pathologic changes in the brain and the psychosis. Aside from mere association, the chief argument for the theory that pernicious anemia has a causal relationship to the psychosis is the frequent occurrence of an "anxious-paranoid" picture, which, as Francke says, "has been too often described in association with pernicious anemia to be a coincidence." The proponents of the theory that pernicious anemia is an important factor in the production of the associated psychosis admit that there is often no mental improvement with liver therapy, but they attribute this, as in the case of persistent symptoms referable to the spinal cord, to the existence of irreversible pathologic changes. From a study of seventy-six cases of pernicious anemia Osgood finds little unequivocal evidence to support the assumption that pernicious anemia can cause psychoses or that mental changes may be a manifestation of pernicious anemia in the same sense as may neurologic changes. Few patients with pernicious anemia have psychoses, and, of those who do, almost half have a predisposition to mental illness, as indicated by the family or past history. While a few of the cases might lead one to think that there is a close correlation between the physical and the mental changes, the evidence is far from being conclusive. Failure of the mental symptoms to improve might be due in some instances to complications such as arteriosclerosis, and in others it may be explained on the theory of irreversible pathologic changes, but one would expect the patients in whom the psychosis did clear to show a closer correlation between the physical and the mental improvement. The majority of the reported psychoses associated with pernicious anemia are of the anxiety paranoid type, but this does not necessarily indicate an etiologic relationship. The preponderance of acute over chronic types of psychoses may be only apparent, since the association of pernicious anemia with chronic psychoses would probably be presumed to be incidental and would not lead to the reporting of such cases. The preponderance of depressive and paranoid manifestations may be explained on the

ground that the physical symptoms of pernicious anemia, the weakness, paresthesias, incoordination, etc., would serve to color the mood or form the basis for paranoid ideas. Manic psychoses in association with pernicious anemia are notably rare. They occurred in only four of the seventy-six cases reported here. The association of psychoses with pernicious anemia is probably largely incidental.

EDITOR'S ABSTRACT.

CEREBRAL VASCULAR ACCIDENTS UNASSOCIATED WITH CARDIOVASCULAR DISEASE. J. ST. C. ELKINGTON, Lancet **1**:6 (Jan. 5) 1935.

Elkington discusses acute cerebral disturbances in healthy young adults which have the general characteristics of vascular accidents. The onset is sudden; the symptoms rapidly reach their climax, and subsequently, if the patient does not die, gradual recovery takes place, leaving some degree of permanent damage. Yet no evidence of cardiac or vascular disease can be found, and the precise pathologic condition remains in doubt. Elkington reports four cases illustrating this condition in all of which the patient lived but continued to have some neurologic signs.

Elkington then describes a somewhat similar case in which symptoms of cerebellar involvement were present. A suboccipital exploratory operation was performed, after which the patient died. Autopsy revealed a blood clot, ¾ inch (1.9 cm.) in diameter, occupying the medial three fourths of the left half of the pons and the reticular formation of the pons. Microscopic examination showed that a hemorrhage had occurred into the substance of a preexisting vascular abnormality of the left half of the pons and the middle cerebellar peduncle. This abnormality had the features of a telangiectasis and was not associated with any vascular abnormality elsewhere in the nervous system or in the skin or other organs.

Owing to the favorable outcome, the author says that one can only speculate on the pathologic condition in the first four cases reported. However, the close clinical resemblance of the condition in these cases to that in other cases in which postmortem examination has been carried out led him to the belief that it is probable that the manifestations were caused by hemorrhage into a vascular anomaly of the type of telangiectasis or arteriovenous angioma.

WATTS, Washington, D. C.

PALLIDAL SYNDROME WITH HYPERKINESIA AND FORCED THINKING AS AN AFTERMATH OF NITROBENZENE POISONING. ALEXANDRA ADLER, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:341, 1934.

The case reported is that of a chemist, a Frenchman, aged 26, who was admitted to the psychiatric clinic with the diagnosis of melancholia. He worked with soaps and perfumes and made use of nitrobenzene. He was well until June 1933. On June 16 he was brought to the house in a drunken condition. His mother, who was much disturbed by this, drank several mouthfuls of Mirbanöl, a nitrobenzene compound. In his emotion at seeing his mother drink this he emptied the rest of the glass, following which he became unconscious. Both were taken to the hospital, where the mother died two days later. The patient showed the typical manifestations of nitrobenzene poisoning on admission. The skin was bluish from formation of methemoglobin in the blood. He was unconscious for four days. The entire body became stiff, and for two months he was unable to walk well. The rigidity gradually decreased, and there developed a tremor in inactivity which lasted for a few months. Finally, facial rigidity and a poverty of movement occurred, which have decreased only slightly.

On admission to the psychiatric clinic the patient was apathetic. He played chess all day. Libido gradually decreased. His attitude toward alcohol changed; whereas formerly he was a heavy drinker, he had no desire for it. Several months after the poisoning he noted a disturbance in writing, which has not improved greatly. He noted that the letters became smaller as he wrote and ended in a line. This varied from time to time, and the patient could not alter it despite his

desire to do so. This micrographia was first described in detail by Pick in syphilitic disease of the brain. It has since been described in cases of paralysis agitans and of other diseases with the akinetic rigid symptom complex. As a postencephalitic manifestation, the disturbance has been described by Gerstmann and Schilder. It has been ascribed to disturbance of the pallidonigral system. Foerster first ascribed micrographia to the pallidal diseases. The symptom did not appear until several weeks after the original poisoning. This is in agreement with what is seen in cases of postencephalitis.

In September, after discharge from the hospital, the patient suddenly began to have obsessional thoughts. During these episodes his mother came into his mind, and he could not think of anything else at that time.

The author summarizes the findings of rigor, tremor, lack of expression, poverty of movement and micrographia as the clinical picture of the hypokinetic pallidal syndrome described by Foerster, Hunt, Kleist, Vogt, Wilson and others, due to a bilateral lesion of the pallidum, with disturbance of the substantia nigra. In addition, involuntary movements occurred, such as scratching and spitting, as hyperkinetic manifestations of an irritative character, as described by Gerstmann and Schilder. The obsessional thinking is considered as a psychic analog of the irritative hyperkinetic manifestation. It has been described as occurring in postencephalitic states by Mayer-Gross and Steiner.

Many deaths have followed nitrobenzene poisoning. The author compares its action with that of carbon monoxide. The lethal dose is variable; it has been fatal in from a few drops in some cases to as much as 35 Gm. in others. No microscopic examinations have been made. Nitrobenzene, however, has been known not only as a blood but also as a nerve poison. Only an occasional case has been reported of the late results from nitrobenzene poisoning. In 1914, Gräfe and Homburger reported deterioration with a Korsakoff syndrome which resembled in many respects that seen after carbon monoxide poisoning. A similar case was reported by Wolpe in a girl, aged 12, whose spine and extremities became rigid after the poisoning. Glycosuria was found, which is not infrequent after carbon monoxide poisoning.

The author considers the manifestations as due to a hyperkinetic pallidal syndrome with obsessional thoughts as the after-result of nitrobenzene poisoning. The condition was not influenced by the administration of scopolamine and atropine.

WINKELMANN, Philadelphia.

A CLINICAL STUDY OF CATAPLECTIC SEIZURES. SCHARFETTER and THOMAS SEEGER, Ztschr. f. d. ges. Neurol. u. Psychiat. **153**:37 (June) 1935.

An unusually thorough clinical study of a single case of cataplexy is recorded. A man, aged 26, in perfect health, was suddenly seized with attacks of muscular hypotonia, especially while sneezing or laughing. He also suffered from insomnia and had an especially vivid dream life. Three months after the onset of the attacks he noted that he would make mistakes while typing, though he was not aware of going to sleep at the time. No period of protracted somnolence was noted. In the fifth month after the beginning of the illness he noted fleeting diplopia once or twice at the beginning of an attack.

Affective stimuli precipitated attacks, especially if the stimuli were sudden and unexpected. The suddenness was apparently a more potent factor than the intensity of the affective experiences. Prolonged affective turbulence did not have a similar effect. Laughing, however, had a progressively severe influence on the incidence of attacks. The affective accompaniment of laughter alone precipitated an attack; tickling and coughing also brought on seizures. Scharfetter and Seeger describe for the first time in medical literature the occurrence of cataplectic attacks after sneezing. The patient was unable to talk loudly or shout, for such activity inevitably resulted in marked hypotonia. The authors emphasize the cataplectogenic rôle of what they choose to call parapneic processes, such as laughing, shouting, sneezing and coughing. The attacks were not prevented by cocainization of the throat and larynx. Sneezing precipitated attacks, even after total

anesthetization of the nose and throat. Pressure on the carotid sinus had no effect. Any muscular effort, especially walking, resulted in hypotonia. Bending the knee produced an attack. If the patient encountered some one suddenly in the street he would have to stop, as the muscular activity and the affective shock resulting from such a chance meeting would surely result in his falling to the ground. Avoiding further muscular activity apparently prevented an attack. Some of the cataplectogenic factors already mentioned were at times not intense enough to bring about an attack. These influences, however, did lower the threshold, so that stimuli of lesser intensity were soon effective. Attacks by themselves also altered thresholds in this way. The authors believe that the so-called *vertige laryngé* described by Charcot, of which there were reports of about 150 cases in the literature up to 1928, consists of cataplectic seizures, probably precipitated by stimuli to the laryngeal nerve.

Neurologic examination gave negative results between attacks, though the pupils were somewhat miotic. There was inconstant but definite constriction of the pupils during an attack. The tendon reflexes were not tested during the severest attacks. The muscles were definitely hypotonic. The muscular weakness was in the nature of an akinesis rather than a real paresis, resembling the state of the musculature during sleep or just as soon as one awakens from sleep. The speech was always affected, being usually soft and feeble.

Medical examination revealed a pyknic habitus, with moderate adiposity and definite evidence of vagotonia during an attack. There was no evidence of hypophyseal involvement or gonadal dysfunction. The patient showed evidence of vagotonia between attacks and increased parasympathetic tonus during an attack. The symptoms of vagotonia were: respiratory arrhythmia, defective carotid sinus, and Aschner reflexes, a low blood sugar content during fasting, a feeble rise in the blood sugar after subcutaneous injections of epinephrine, mild lymphocytosis in the blood and a low sedimentation time.

The authors note the excellent response to ephedrine. The average dose was from 0.025 to 0.050 Gm. three times a day. When the drug was omitted, the attacks inevitably returned. Toxic manifestations of this drug were minimal. The site of action of the drug is probably peripheral and the nature of its action is that of toning up of the effector mechanism. At the same time the effect of ephedrine on the circulation may result in the supply of an increased amount of blood to the brain and a heightened metabolism. It may also be effective in relieving the adrenal glands of some of their work.

The cataplectic attack has much in common with sleep and is considered by the authors a fragment of the sleep complex, its motor component. Cataplexy can, however, be considered a latent motor reaction pattern most commonly noted in sleep but also available in response to other stimuli (sudden fright and sham death reflex in animals). The authors postulate a reflex mechanism through the vagus nerve on the tonus centers. SAVITSKY, New York.

Peripheral and Cranial Nerves

OCULOMOTOR NERVE SPASM IN GRADENIGO'S SYNDROME. ABRAHAM FINE, Arch. Otolaryng. **21**:142 (Feb.) 1935.

Attention is called to the fact that the ophthalmologic features of Gradenigo's syndrome have not been described as fully as the otologic signs. The sensory branches of the fifth and the sixth nerve are regularly involved; the second, third, fourth and seventh nerves are sometimes involved, even when there is no evidence of extension of the process intracranially to account for the involvement of the nerves. It should be clearly understood that involvement of these nerves may be transitory, just as the characteristic triad of Gradenigo may be transitory after a simple operation on the mastoid. Therefore, a choked disk per se is not an indication for surgical intervention, nor is paralysis of the face due to involvement of the seventh nerve, or vertical diplopia due to involvement of the fourth

nerve necessarily an indication of serious intracranial involvement. The special point which Fine makes is that the third nerve is frequently involved in Gradenigo's syndrome, resulting in a spasm of the homolateral internal rectus muscle. He states that this spasm is not seen in cases of paresis of the sixth nerve but that in a case of complete palsy of the abducens nerve spasm may make its appearance as early as the first week. The diagnosis of spasm of the internal rectus muscle due to irritation of the third nerve is made as follows: When a patient with simple paralysis of the sixth nerve, which involves the external rectus muscle, looks forward, the affected eye is straight, the internal squint being noticed only when the patient looks in the direction of the affected external rectus muscle. When spasm of the internal rectus muscle is present, there is an internal squint when the patient looks straight ahead with the affected eye. The spastic muscle moves the eye in adduction more quickly than the normal eye. A patient with a spastic internal rectus muscle has diplopia. On looking to the extreme periphery in the direction of the spastic muscle, when no effect from the paralyzed external rectus muscle would be noticed, he also has diplopia. If no spasticity were present, the patient would not have diplopia on looking in this direction. When one sixth nerve is paretic and the other paralyzed, the differentiation between bilateral involvement of the sixth nerve and homolateral involvement of the third and sixth nerves depends almost entirely on a study of diplopia. In a case of homolateral involvement of the right eye the diplopia was less marked when the patient looked to the left than when the eyes were in the primary position, and during recovery diplopia to the left was the first to disappear. In cases of bilateral involvement of the sixth nerves, diplopia and internal strabismus are less marked when the eyes are in the primary position than when they look either to the right or to the left.

HUNTER, Philadelphia.

APIOL POLYNEURITIS. ROBERT DENISON and J. C. YASKIN, J. A. M. A. **104**:1812 (May 18) 1935.

Denison and Yaskin report a case of polyneuritis caused by apiol (Parsley camphor). The subject of polyneuritis following the use of apiol is well described by ter Braak and Carrillo, who collected reports of thirty-seven cases from the literature and reported thirteen cases from Holland. The condition in the authors' case differs somewhat from the European variety. At the outset there were severe gastro-intestinal symptoms and marked reactions of the skin and mucous membrane, which are not mentioned in the literature. The duration of the latent period was twenty-one days. The neurologic involvement was somewhat more extensive than in the cases reported in the European literature, appearing, however, preeminently motor, distal and symmetrical. The fact that the patient ingested an exceedingly large dose of the drug in a short period of time may help to account for the severity of the symptoms. All the cases reported would tend to show that the process is limited to the peripheral nerves and that there is no involvement of the central nervous system. This neuritis is due not to apiol but to tri-orthocresyl phosphate, which is contained in the abortifacient. Apiol, which is an extract of parsley, is in itself nontoxic. The fact that tri-orthocresyl phosphate is capable of producing neuritis has been known for a long time. The clinical courses of patients treated for pulmonary tuberculosis, for jamaica ginger paralysis and for polyneuritis due to the ingestion of apiol show almost the same characteristics. The condition in the authors' case resembled the jamaica ginger type of paralysis. The pathogenesis of neuritis due to tri-orthocresyl phosphate appears to depend on the selective action of the toxic substance on the myelin sheaths of the peripheral nerves with secondary degeneration of the axis-cylinders (periaxillar neuritis). In addition to the peripheral nerves of the extremities, tri-orthocresyl phosphate is reported to have caused retrobulbar neuritis.

EDITOR'S ABSTRACT.

STUDIES ON LIVING NERVES: III. PHENOMENA OF NERVE IRRITATION AND RECOVERY, DEGENERATION AND REPAIR. CARL CASKEY SPEIDEL, J. Comp. Neurol. **61**:1 (Feb.) 1935.

In previous publications Speidel described the movements of the cells of Schwann and of nerve sprouts, the process of the formation of myelin sheaths and the activities of the growing tips of single nerve fibers. He here presents a study of irritation of nerves and recovery, degeneration and repair as revealed by direct observation of the individual fiber in the intact living organism. These observations were aided by the use of the micropolariscope and of motion pictures. The experiments included study of both acute and chronic types of irritation as well as of intermediate kinds. The irritation was either focal or general. Practically all grades of injury were noted from slight swelling to total degeneration. Many diverse methods were employed for the induction of irritation, such as sectioning, burning, the use of anesthesia, treatment with alcohol, roentgen irradiation, the application of pressure and the administration of thyroid extract. The length of the time of irritation varied from a few minutes to several weeks. The changes that characterize irritation of a nerve bore a marked resemblance to the early changes that characterize trophic (wallerian) degeneration after section of a nerve. In a segment of myelinated fiber, irritated by an adjacent wound which did not sever the nerve, there was immediately a pronounced swelling between the myelin sheath and the axis-cylinder. The nuclei of the cells of Schwann became swollen and were intimately applied to the myelin sheath. If the irritation was strong, degeneration followed with the formation of myelin ovoids and granules. Great variation was noted in the speed and violence of irritative change. Scalding with hot water caused immediate and powerful irritative changes in the segments of myelinated fiber bordering the injured zone. Similar though slightly less rapid effects were noted after injuries caused by treatment with alcohol, a strong anesthetic, pressure, freezing and acids or alkalis. In the case of lesser injuries the irritative effects exhibited by the nerves were not so pronounced. Chronic irritation was accompanied by still slower irritative changes. Treatment with an extract of the thyroid gland changed straight nerves into wrinkled nerves. Wrinkling of the fibers also occurred after section of a nerve. Degeneration of the myelin sheath was always seen to accompany the degeneration of the enclosed axis-cylinder. On the contrary, the axis-cylinder sometimes remained fairly normal when the myelin sheath degenerated.

Among the varieties of regeneration that have been recorded are: (*a*) growth of unmyelinated fibers along entirely new routes; (*b*) growth of unmyelinated fibers to join old paths, with extension along these in both directions; (*c*) growth of unmyelinated fibers from a plexus junction in a reverse direction along a degenerating path; (*d*) formation of anastomoses between growing tips of unmyelinated fibers, and (*e*) growth of myelinated fibers from nearby uninjured nerves to supply denervated tissues. Complete experimental isolation of the cells of Schwann from nerves has been accomplished with both myelinated and unmyelinated fibers. Other observations include variations in extension of the growth cones, irritation of the nerve endings, variations in the rate of the adjustment of the myelin sheath correlated with the type of injury and repair and movements of leukocytes in degenerating, normal and regenerating nerves. With the aid of the micropolariscope the behavior of the anisotropic substance of the myelin sheath has been investigated during the process of myelinogenesis and during irritation, degeneration and regeneration of the nerve.

ADDISON, Philadelphia.

OBSERVATIONS ON REFERRED PAIN. CHARLES BOLTON, Brain **57**:211 (Oct.) 1934.

Bolton advances evidence that pain and tenderness associated with gastric and duodenal ulcer are of the referred visceral type. He does not discuss the question whether splanchnic pain occurs in addition. Older clinical observers recognized the presence of referred pain. Ross (1883) clearly distinguished this referred, or somatic, pain from splanchnic pain conveyed by afferent sympathetic nerves

from the organ which is the seat of the disturbance. It remained for Mackenzie (1892) to give the first objective evidence in favor of the theory by drawing attention to associated tender areas in the body wall, cutaneous hyperesthesia and reflex muscular irritability. His most important observation as regards the abdomen was that by which he proved that the tender areas in patients with gastric ulcers occurred in positions different from those of the ulcers themselves. Morley (1931), however, claimed that Mackenzie's observations are untrue and that the position of the tender area corresponds with that of the ulcer. He found that the tender point shifted with changes in the position of the ulcer and therefore concluded "that the tenderness is not produced by a 'reflex' or radiation through the afferent splanchnic fibers, since that hypothetical process could only give rise to a fixed and immobile tenderness, the position of which would be determined not by the position of the ulcer in relation to the abdominal wall but by the distribution of those sensory nerves in the abdominal wall which entered the same segment of the cord as received the afferent autonomic nerves from the ulcer." The tenderness over the ulcer is, according to Morley, felt in the overlying skin and subcutaneous tissue as a reflex in response to stimulation of the parietal peritoneum in contact with the ulcer.

Bolton draws attention to the importance of the manner of determining tender areas. He cites the deep pressure of the roentgenologists who press the anterior abdominal wall against the ulcer, demonstrating the ulcer itself to be tender, as compared with the light palpation of the clinician in his demonstration of abdominal tenderness.

In his Croonian lectures (1928) Bolton reported the results of an analysis of 1,000 cases of gastric pain; in 715 of these pain was exhibited in a single area, the pain being in the sterno-umbilical region in 533, in the midline in 452 and at the costal margins in 81. Most of the tender points occurred in a central line drawn between the umbilicus and the ensiform cartilage. On this line there are three areas, each about 2.5 cm. in diameter, namely: (1) at the center where the transpyloric line joining the right and the left ninth costal cartilage cuts it, (2) above this point, just below the ensiform cartilage, and (3) below it, near the umbilicus. These three points correspond to the seventh, eighth and ninth thoracic segments, which probably overlap (Head and Foerster). There are three further points situated in these segments lateral to the central points just described, namely: (1) in the ninth thoracic segment, a few centimeters to the right or left of the central line; (2) in the eighth segment in the costal margin over the right and left costal cartilages, more commonly on the right, and (3) in the seventh thoracic segment at the upper portion of the left costal margin, rarely on the right side.

The first and most important objective was to determine definitely the relation of the position of these tender areas to the positions of the ulcers as seen in the roentgenograms. The series investigated comprised 25 cases of gastric ulcer, 13 cases of duodenal ulcer and 13 cases of painful gastric neurosis. The presence of all the ulcers was confirmed roentgenographically, and there was said to be tenderness on deep palpation in all instances. In the cases of gastric neurosis the stomach was proved to be normal by roentgenographic study and was free from tenderness.

The following method of investigation was followed. The tender areas were determined with the patient in the upright and then in the supine position and marked on the surface of the skin. In every case the results were exactly the same in the two positions. A glass screen was placed on the abdomen, and the positions of the costal margins, the umbilicus and the tender areas were marked on it. The umbilicus was then marked with a piece of metal, a barium sulfate meal was given, and roentgenograms were taken immediately with the patient in the erect and then in the supine position. The x-ray films were placed under the glass screen so that the landmarks corresponded. The position of the ulcer as demonstrated by the roentgenogram was then marked on the glass screen. The distances of the ulcers from the midline, above or below the umbilicus, could then be computed. The results obtained were: Of the 25 cases of gastric ulcer, in all but 2

the tender area involving the small curvature was situated in the central sterno-umbilical line, in the center of this line, above the center or below. In all the point was constant in position whether the patient stood erect or lay supine. In all but 1 case the ulcer shifted upward when the patient assumed the supine position. In 21 cases the tender point was situated in a different position from that occupied by the ulcer when the patient was in both the erect and the supine position. The tender point remained the same whatever the position of the patient, whereas, in contrast, the ulcer moved upward when the patient was in the recumbent position. The evidence was inconclusive in the 2 cases of pyloric ulcer. In the other case the tender point was situated in the midline below the ensiform cartilage, whereas when the patient was in the erect position the ulcer was situated in the midline 3 cm. below the umbilicus, and when he was in the supine position it had shifted upward and outward. In the 13 cases of duodenal ulcer, the tender point in 11 cases was situated in the midline and at its upper, middle or lower portion. In 3 of these 11 cases there was an associated tender point at the right or left costal margin or both. In 2 cases of duodenal ulcer only the area at the margin of the right ninth costal cartilage was tender. In every case the position of the ulcer with the patient in the erect position was to the right of the midline; in 8 cases it was above the umbilicus; in 3 cases on a level with the umbilicus, and in 2 cases below the umbilicus. With the patient in the supine position, the ulcer was to the right of the umbilicus and occupied a higher position than with the patient in the standing position. In these 13 cases the tender point obtained by light palpation was situated at a different level from that occupied by the ulcer with the patient in both the erect and the supine position. In the 13 cases of gastric neurosis, Bolton found an area of tenderness in the anterior abdominal wall in positions exactly similar to, and indistinguishable from, those described in the cases of ulcer.

From the recorded observations, Bolton states that the tender areas present in the abdominal wall in cases of functional disorder of the stomach are of the same nature and origin as those which occur in cases of gastric and duodenal ulcer. These tender areas are fixed and immobile and are independent of any change in the position of the patient and thus have no relation to the position of the stomach. He states: "They have, therefore, the characters of referred pain and tenderness due to abnormal impulses originating in the viscus, which are conveyed to the spinal cord by its afferent sympathetic nerves, and their positions are determined by the distribution of those muscular and cutaneous nerves in the body wall which enter the same segments of the cord as receive the afferent sympathetic fibers from the stomach."

The fixed position of pain and tenderness is explained as a result of Bolton's analysis of gastric pain, in which he found that the areas of pain were most commonly situated in the region of four vertical lines: (1) the midline in front; (2) a line through the nipple and costal margin, sometimes in the region of the ninth costal cartilage or sometimes higher up; (3) the line of the angle and vertebral border of the scapula, and (4) the midline behind, especially between the scapulae. He states that it is in these lines that the terminals of the thoracic nerves which supply both the skin and the underlying muscles are distributed. He reviews briefly the origin and distribution of these nerves and shows that they terminate in the four vertical lines corresponding to the areas in which he found pain to occur most commonly. This explanation of the distribution of pain, Bolton states, holds good only if the irritation giving rise to the pain is situated in the spinal cord or at the origin of the nerve trunks at the terminals of which the pain and tenderness are felt. That the pain and tenderness are segmental in distribution and occur in the region of these nerve terminals Bolton thinks is strong support of the hypothesis that the point of irritation is in the spinal cord, this focus of irritation being due to afferent impulses received through sympathetic nerves from the stomach.

SALL, Philadelphia.

RUPTURE OF THE ROOTS OF THE BRACHIAL PLEXUS IN TRAUMATIC RADICULO-FUNICULO-PLEXITIS. V. CHOROSCHKO, Encéphale **30**:126, 1935.

Six cases of posttraumatic paralysis of the brachial plexus are reported, diagnostic tests with iodized poppy-seed oil 40 per cent being carried out with the patient lying on his side. The trauma was always severe and involved the nerve roots. In one case the transit of the iodized oil was normal. In spite of complete paralysis of the upper limb, with muscular atrophy, enophthalmia, etc., a favorable prognosis was given and "confirmed by later observation," of which no detail is given. In the five other cases the iodized oil was arrested at the level of the different cervical nerve roots on the affected side (the seventh in three cases, the fifth and sixth in one case and the eighth in one case) and formed large rounded drops which protruded beyond the limits of the dura. The conclusion was that the corresponding roots were ruptured at or near their emergence from the dura. In none of these cases was there any notable improvement during periods of observation varying from four months to over a year. In two cases iodized oil seemed to fill a cavity or cyst when the patient was lying on his side, but reentered the dura and fell freely to the bottom of the sac when the patient sat up. In one of these cases laminectomy showed an oval extradural cyst, containing clear fluid. Intradural radicular rupture is more frequent than most clinicians believe. The diagnosis and localization can be asserted only after examination with iodized oil.

LIBER, New York.

CANCER OF THE ESOPHAGUS WITH BILATERAL RECURRENT PARALYSIS OF THE LARYNGEAL NERVE; ATYPICAL EVOLUTION: CANCEROUS ENGRAFTMENT ON THE EPIGLOTTIS. F. J. COLLET and R. MAYOUX, Rev. d'oto-neuro-opht. **13**:194 (March) 1935.

A case of cancer of the esophagus with bilateral recurrent paralysis of the laryngeal nerve is reported. One of the interesting facts in this case is the atypical evolution of the paralysis. The right vocal cord was in the intermediate position in the beginning; later it was fixed in the median position, with return of the voice, and then it returned to the intermediate position. The only reasonable explanation of this phenomenon is the unequal and variable pressure of the tumor on the nerve filaments. Another point of interest is the grafting of the cancer on the epiglottis. This was probably the result of repeated esophagoscopy, which chafed the epiglottis and favored the transplantation of the cancerous material. The histologic appearance of the piece removed at biopsy was that of a rapidly diffusing surface lesion, propagated by way of the vessels.

DENNIS, San Diego, Calif.

Cerebrospinal Fluid

THE RELATION OF NEGATIVE PRESSURE IN THE EPIDURAL SPACE TO POSTPUNCTURE HEADACHE. WILLIAM M. SHEPPE, Am. J. M. Sc. **188**: 247, 1934.

Sheppe has observed that patients in whom spinal puncture is performed most easily are more liable to have postpuncture headache. Patients in whom the needle enters the subarachnoid space at a single thrust have headaches in a larger proportion of cases than patients in whom one inserts the needle several times, withdrawing the stylet at each attempt. He noted that in punctures in which some difficulty is experienced in entering the dural sac, or if for any reason the stylet was withdrawn from the needle before the dural sac was entered, often a slight but distinct hissing sound was heard, as if there were a sudden inrush of air into the needle.

From a review of the literature and his own observations, Sheppe considers continued leakage of spinal fluid from the dural sac the predominant cause of postpuncture headache. Ayer, who injected lampblack into the cistern of cats, demonstrated that such leakage does occur. Nelson noted that the spinal fluid pressure

after the development of headache was lower than after the withdrawal of fluid at the end of the first puncture. Heldt and Maloney have found evidence of negative pressure in the epidural space varying from — 1 to — 18 mm. of mercury. Correlating his own findings with those in the literature, Sheppe considers continued leakage of spinal fluid due to negative pressure in the epidural space. Since adopting measures to counteract the negative pressure and continued leakage of fluid, he has greatly reduced the incidence of postpuncture headache. In the last one hundred examinations done on ambulant patients, three complained of slight headaches on the day following puncture.

"Since we have adopted: (1) The use of a needle not greater than 22-gauge with a sharp tapered point; (2) the practice of slow withdrawal of the needle, without replacing the stylet, with full time allowance for the entry of air to the subdural space, we have been able almost completely to obviate the complication of severe postpuncture headache."

WATTS, Washington, D. C.

DISSOCIATIONS IN CEREBROSPINAL FLUID FINDINGS: REPORT OF A NEW TYPE (GLOBULINOCOLLOIDAL DISSOCIATION). V. KAFKA, Schweiz. Arch. f. Neurol. u. Psychiat. **23**:15, 1934.

After enumerating the various instances of lack of parallelism between the results of different tests of the cerebrospinal fluid, Kafka reviews the work of his assistant, Samson, on globulin-colloidal dissociation, a term implying a negative colloidal reaction in the presence of an increase in the globulin content. Although globulin is the precipitating agent in positive colloidal reactions, in some conditions, notably tumor of the brain, the latter reaction may be negative in spite of a markedly increased globulin content. In cases of cerebrospinal syphilis, particularly the form typical of dementia paralytica, on the other hand, a very slight increase in the amount of globulin may bring about a pronounced precipitation in the mastic test. The mastic reaction depends, therefore, more on the quality than on the quantity of the globulin present. A considerable increase in the amount of albumin tends to inhibit the precipitating action of globulin, but in the cases under consideration the concentration of albumin was either normal or only slightly increased.

DANIELS, Denver.

PRESSURE OF THE CEREBROSPINAL FLUID IN CASES OF EPILEPSY. A. BOTELHO, Arq. brasil. de neuriat. e psiquiat. **16**:14 (July-Aug.) 1933.

Botelho says that Ayala's quotient for the determination of the pressure of the cerebrospinal fluid oscillates between 5 and 7 in normal persons. It is above 7 in epileptic patients. The higher figures are obtained for those patients who suffer from frequent convulsive attacks, and still higher figures for those in whom the quotient is determined during a crisis. These facts indicate the advisability of withdrawing the cerebrospinal fluid of epileptic patients both during the attack, with the aim of diminishing its intensity, and in the intervals between the crises, with the object of diminishing the frequency of their appearance.

EDITOR'S ABSTRACT.

CLINICAL EXPERIENCES WITH KAFKA'S METHOD FOR DETERMINING THE PROTEIN RELATIONSHIPS IN THE SPINAL FLUID. F. LEIP, Monatschr. f. Psychiat. u. Neurol. **87**:305 (Jan.) 1934.

Leip reports the results of a study of 600 specimens of spinal fluid by means of the Kafka method for the determination of the relative amounts of albumin and globulin. In cases of dementia paralytica there was usually a marked increase in the total amount of protein, which was due chiefly to a high globulin content of the spinal fluid. Hence the protein quotient, obtained by dividing the value for globulin by that for albumin, is raised. An increase in the amount of globulin occurred in cases of dementia paralytica of the tabetic form and in cases of tabes

and cerebrospinal syphilis, but progressively increasing amounts of albumin were also found in these conditions in the order named and thus progressively decreasing protein quotients. Even in cases of cerebrospinal syphilis, however, the quotients remained above normal. After treatment the total amount of protein tended to diminish, largely owing to a decrease in the amount of globulin. This diminution was frequently but not invariably most pronounced in the cases in which there was clinical improvement. While there was no constant relation between the alterations in the protein content and other changes noted in the spinal fluid, the protein quotients and the colloidal gold curves often exhibited a considerable degree of parallelism. In cases of meningitis the quotients were normal, though the values for the total amount of protein were high. An increase in the amount of albumin was chiefly responsible for the high protein content of the spinal fluid associated with Froin's syndrome. In cases of Landry's paralysis, myelitis, hematomyelia, funicular myelopathy and postencephalitic parkinsonism the total amount of protein had as a rule moderately increased, with the changes predominating in the albumin fraction. Specimens of fluid obtained in cases of acute poliomyelitis and in cases of tumor and abscess of the brain usually showed alterations of the protein quotients, but these were inconstant. In most cases of multiple sclerosis there was a relative increase of globulin with a slightly increased quotient. Minor alterations of the quotients were not uncommon in cases of senile dementia and cerebral arteriosclerosis. After injuries to the head, the spinal fluid frequently presented an excess of albumin with a consequent rise in the values for the total amount of protein. These changes may be the only indication of organic damage to the central nervous system. In cases of uncomplicated chronic alcoholism the albumin content of the spinal fluid was moderately increased. In almost half the cases of genuine epilepsy the figures for the total amount of protein were above normal, the changes predominating in the albumin fraction. More than a third of patients with schizophrenia presented high values for the protein content in the spinal fluid. As a rule the alterations were caused by an increase in the amount of albumin. The great majority of the determinations made in cases of manic-depressive psychosis and symptomatic psychoses yielded normal results. In more than half the cases of psychopathic personality the spinal fluid showed high figures for protein, with albumin contributing chiefly to the increase.

ROTHSCHILD, Foxborough, Mass.

COMPARATIVE STUDIES OF CEREBROSPINAL FLUID OBTAINED BY CISTERNAL AND BY LUMBAR PUNCTURE IN NERVOUS AND MENTAL DISORDERS. F. KULCSÁR, Monatschr. f. Psychiat. u. Neurol. **88**:87 (Feb.) 1934.

In normal persons cerebrospinal fluid obtained by cisternal puncture shows only minimal differences from that obtained by lumbar puncture. The values for sugar are somewhat higher and the cell counts slightly lower in the former than in the latter. These differences may be more marked in diseases of the central nervous system. In cases of syphilis the colloidal gold curve may show less pronounced abnormalities and the Wassermann reaction may be less strongly positive with fluid obtained by cisternal puncture. If allowance is made for such variations, a study of the fluid obtained by cisternal puncture will disclose information which is equal in value to that revealed by a study of the fluid obtained by lumbar puncture. In cases of nervous and mental diseases cisternal puncture is the method of choice because it rarely leads to meningism. Lumbar puncture may be performed later if special conditions, such as local disease of the spinal cord, render that procedure advisable.

ROTHSCHILD, Foxborough, Mass.

CHANGES IN THE CEREBROSPINAL FLUID OF DOGS AFTER REPEATED CISTERNAL PUNCTURES. E. M. STEBLOW and A. B. MANDELBOIM, Monatschr. f. Psychiat. u. Neurol. **88**:104 (Feb.) 1934.

Cisternal punctures were performed on twelve dogs; three days later they were repeated on nine of the animals. In seven of the dogs cerebrospinal fluid was

withdrawn seven days later, and in a smaller number it was withdrawn fifteen, twenty and twenty-five days after the first test. The specimens of fluid obtained for the second series of tests showed xanthochromia, a meningitic type of colloidal gold curve in two thirds of the specimens and an average of 47 cells per cubic millimeter and 65.3 mg. of protein and 79 mg. of sugar per hundred cubic centimeters, as compared with 3.75 cells per cubic millimeter and 24.8 mg. of protein and 83 mg. of sugar per hundred cubic centimeters in the spinal fluid obtained for the first series of tests. Later cisternal puncture yielded fluid with a normal sugar content and a gradual reduction in the number of cells, the final tests yielding specimens of spinal fluid which showed an average of 21 cells per cubic millimeter. The colloidal gold curve and the protein content of the cerebrospinal fluid returned to normal in the fourth and fifth series of tests, respectively. Steblow and Mandelboim conclude that the changes are due to irritation of the meninges with hyperemia of the meningeal vessels. The increase of cells is based largely on their phagocytic activity and on a lowering of function of the meningeal and the vascular barrier.

ROTHSCHILD, Foxborough, Mass.

THE CHANGES IN THE SPINAL FLUID IN PATIENTS WITH ENDOGENOUS PSYCHOSES AND THEIR SIGNIFICANCE IN DIFFERENTIAL DIAGNOSIS. PAUL KOPP, Ztschr. f. d. ges. Neurol. u. Psychiat. **151**:656 (Dec.) 1934.

In 50 per cent of 153 schizophrenic patients the spinal fluid was entirely normal. An increase in the total amount of albumin and of globulin, precipitation of colloids and an increase in the cholesterol content were found in 55 other schizophrenic patients. In 19 acutely ill patients the number of cells was increased. The spinal fluid of 17 patients with cyclothymic depressive psychoses was normal. It is concluded that an increase in the total amount of albumin, globulin or cholesterol or in the number of cells in the spinal fluid of a patient with a psychosis indicates a complicated process, e. g., traumatic disease of the central nervous system, cerebral arteriosclerosis, epilepsy or syphilis and that absence of blood in the spinal fluid indicates a schizophrenic process.

MICHAELS, Boston.

THE EFFECT OF NUTRITION ON THE VITAMIN C CONTENT OF THE SPINAL FLUID AND THE POSSIBILITY OF DIAGNOSING C-HYPOVITAMINOSIS BY EXAMINATION OF THE SPINAL FLUID. F. PLAUT and M. BULOW, Ztschr. f. d. ges. Neurol. u. Psychiat. **152**:324 (March) 1935.

The average vitamin C content of the cerebrospinal fluid was determined for a series of control subjects. It varied definitely with the age of the subject; for those between 20 and 35 years of age it was 1.77 mg. per hundred cubic centimeters; for those between 36 and 59, 1.97 mg., and for those between 61 and 83, 0.51 mg. Plaut and Bulow observed progressive diminution in the vitamin C content of the spinal fluid of four patients with schizophrenia and of one mentally defective person during their residence in a hospital for patients with mental disease. In one case the vitamin C content of the spinal fluid was reduced to as much as a quarter of its first value in a few months. In the other four cases it was reduced to about 50 per cent of its original value, the reduction in one of the cases taking place after fourteen days of hospitalization. Control studies of the spinal fluid obtained from the same patient at intervals of three days showed that such spontaneous variations were not usual.

The authors report the effect of feeding vitamin C on the vitamin C content of the spinal fluid of human beings. One hour and two and a quarter hours after 300 cc. of orange juice was given by mouth a lumbar puncture was done. No change was found in the vitamin C content of the spinal fluid. Longer periods of feeding with vitamin C were tried for seven, eight and fourteen days, 90 mg. of cevitamic acid being given daily in the form of 9 tablets. The amount of vitamin C given was the equivalent of that in about 150 cc. of lemon juice. All the persons studied had a low vitamin C content of the spinal fluid. In all

a definite increase in vitamin C content was noted after prolonged feeding. A definite increase was noted after seven days and further rises after fourteen days. When the feeding was stopped no decrease was noted for ten days. Three weeks after the cessation of the feeding the values for vitamin C were lower, but not yet normal. The authors conclude from these observations that feeding with vitamin C definitely raises the vitamin C content of the spinal fluid of human beings.

A similar relation was found in rabbits. The vitamin C content of spinal fluid of rabbits is higher in the summer than in the winter because the food eaten during the summer contains more vitamin C. In four rabbits it was demonstrated that by feeding foods containing vitamin C the amount of this vitamin in the spinal fluid could be increased. Cevitamic acid, injected intrathecally, disappeared rapidly from the spinal fluid of rabbits. After the oral administration of this acid to human beings the increased amount of this substance in the spinal fluid did not decrease very readily. One cannot, therefore, conclude much regarding the physiologic chemistry of vitamin C in human beings from experiments on animals. Rabbits probably synthesize their own vitamin C.

Fifty cubic centimeters of lemon juice was fed to a group of rabbits by means of a tube. Spinal puncture was performed on all before the feeding and on groups of two or three at intervals of one, two, three, four, five, six and twenty-four hours after feeding. In none of the animals was there any increase in vitamin C in the spinal fluid. In another group 100 mg. of pure cevitamic acid was injected intravenously. In these animals the vitamin C content of the spinal fluid was increased one-half hour after the injection, and an increased amount was still present twenty-four hours later. The increase was somewhat more than 1 mg. per hundred cubic centimeters.

Differences in the vitamin C content of the diets of young and old patients cannot account for the differences in the amount of vitamin C in the spinal fluid. To prove that the length of stay in the hospital of the older patients played no rôle, spinal puncture was carried out on admission on fifteen patients between 20 and 30 years of age and on fifteen between 55 and 77. The average vitamin C content of the spinal fluid of the younger patients was 2.11 mg. per hundred cubic centimeters, and that of the older patients, 0.60 mg. The length of exposure to hospital diet, therefore, cannot account for the difference in the vitamin C content between the two groups. This difference is not due to defective absorption of the vitamins in the older persons, because in three (ages 64, 74 and 72) the vitamin C content of the spinal fluid increased following the oral administration of the vitamin, just as it did in the younger patients. The conclusion is therefore justifiable that the lower values for vitamin C in the spinal fluid of older persons is due to a decreasing intensity of the metabolic processes concerned with the elaboration of vitamin C.

It was shown in cases of induced malaria that febrile diseases decrease the vitamin C content of the spinal fluid.

The quantitative determination of vitamin C in the spinal fluid, with consideration given to the age of the patient and other modifying factors, such as febrile diseases, can be used as a measure of the C hypovitaminosis.

SAVITSKY, New York.

Experimental Pathology

VITAL STAINING OF MICROGLIA. LESTER S. KING, Arch. Path. **19**:656 (May) 1935.

The lack of reaction of nerve tissue toward colloidal vital dyes, such as trypan blue, has given great support to the concept of a protective barrier between the blood stream and the brain. Other tissues of the body stain freely; the brain does not. This fact is explained by many authors by the so-called hemato-encephalic barrier. That the vascular supply of the brain possesses properties of an entirely different order from those of other organs is a concept of extreme theoretical

and practical importance. But the evidence for this hypothesis, so far as it is drawn from vital staining, is open to another explanation, namely, that the virtual absence of vital staining in the brain is due not to a vascular barrier but to an intrinsic lack of affinity for the dye.

For the study of this problem the vital staining of the microglia offers a fruitful approach. Although under suitable conditions the microglia cells may have certain properties of phagocytosis and ameboid movements in common with macrophages of other parts of the body, there is a profound difference in the reaction to trypan blue. De Asua, who considered the microglia as part of the reticulo-endothelial system, expressed a belief that the normal absence of vital staining of microglia is due to a vascular barrier which withholds the dye.

A different approach to the problem of the nature of the reaction of nerve tissue toward colloidal dyes would be to activate the microglia without simultaneously raising the permeability of the blood vessels. Such a method is offered by the study of secondary degeneration of fiber tracts at a distance from the lesion. The reaction of such degenerating areas is entirely gliogenous in the early and middle stages, with the microglia playing an important rôle.

Observations were made on a series of nine rabbits in which transection or partial transection of the cord was performed under aseptic conditions. The animals were allowed to survive for from eight to fourteen days. During this period from six to ten subcutaneous injections of 5 cc. of a 2 per cent solution of trypan blue were given.

The transition from microglia cells to gitter cells has been frequently described in the literature. The transformation of nonglial elements, such as macrophages, into gitter cells has not received so much attention. In certain instances this transformation could be well followed. At the onset of the reaction the macrophage is heavily laden with granules of trypan blue but shows no fat vacuoles. Gradually more and more of the lipoid material is ingested, causing the cell to become larger and more vacuolated. Simultaneously the granules of dye become more dispersed in the attenuated cytoplasm, and the individual granules appear smaller and more numerous than in the cell without lipoid inclusion. So far as the fat content is concerned, the gitter cell derived from the macrophage is indistinguishable from the same cell derived from the microglia. But the trypan blue content in the former is vastly greater than that of the latter. This is obviously correlated with the greater amount of dye in the macrophages before lipoid phagocytosis has commenced.

The author concludes: "1. The affinity for trypan blue is of a distinctly lower order of magnitude in microglia than in the macrophages of the central nervous system.

"2. A significant proportion of the gitter cells in a wound area arise not from the microglia but from macrophages of the vascular sheaths and of the invading connective tissue.

"3. Microglia far removed from a focus of injury, when stimulated to activity by the process of secondary degeneration, do not store trypan blue."

WINKELMAN, Philadelphia.

EFFECTS OF EXPERIMENTAL LESIONS OF THE POSTERIOR COLUMNS IN MACACUS RHESUS MONKEYS. A. FERRARO and S. E. BARRERA, Brain **57**:307, 1934.

Ferraro and Barrera point out that few experiments have been performed in animals on the dorsal column system, especially in forms such as the monkey. Most of the experiments have been acute and have been inadequately controlled. Macacus rhesus monkeys were used in this study. The columns were usually sectioned, and none of the substance of the dorsal column was removed. No infections occurred in a series of over twenty monkeys. Serial sections of the spinal cord at various levels above and below the lesion were made. In particular, the termination of the degenerated portions of the dorsal columns in the medulla were studied serially.

In the first monkey studied, complete section of the dorsal columns at the fourth cervical segment was performed. Twenty-four hours and also five days after operation there was absence of spontaneous movements of the prehensile type in all limbs, especially in the forelimbs and loss of the sense of position of the limbs. There was a characteristic posture of the forelimbs, which were adducted, semiflexed and motionless, with the hands open. There were absence of spontaneous grip in all limbs, generalized hypotonia, with retention of response to pain and deep touch and loss of the placing and hopping reflexes. The righting reflex, lost the first day after operation, returned later to some extent. At the two weeks stage the animal attempted to walk in a hopping manner, like a kangaroo, the forelimbs remaining useless. One month after operation the animal had a satisfactory gait, with a tendency to retention of hopping, using mainly the hindlimbs. The forelimbs were used to some extent but in a clumsy manner, there being a tendency to slipping out to one side or the other. Three months after operation the animal continued to show slow improvement, especially with regard to the use of its limbs. The forelimbs showed more defect than the hindlimbs, though they were used more in locomotion and in feeding. The maximum improvement occurred between the third and the fourth month, when there developed some ability to climb about on the cage. The main points which characterized the animal at this stage were: deficiency in spontaneous fine grasping movements and in fine coordinated movements of the limbs, clumsiness and stumbling in fast movements, lack of spring in the limbs in jumping, with a tendency toward spreading the limbs, persistence of hypotonia with active deep reflexes and, finally, retention of pain and touch sensibilities. All these deficiencies increased when the animal was blindfolded. Histologically, the lesion had severed the dorsal columns at the level of the fourth cervical segment. Below the lesion there was no evidence of involvement of the pyramidal tracts. Above the lesion there was no evidence of involvement of the dorsal spinocerebellar tracts, and the degeneration of the dorsal columns was complete.

In a second monkey, a lesion was made at the fourth cervical segment so as to divide both columns of Burdach. Two weeks after operation the animal presented hypotonia of the forelegs, with normal tone in the hindlegs. Spontaneous grasping had not returned. The sense of position of the forelimbs was impaired, whereas that of the hindlimbs was normal. Sensation to touch and pain were retained throughout the limbs and body; the deep reflexes were active. The hopping and placing reflexes were absent in the forelimbs and present in the hindlimbs. The symptoms were essentially symmetrical in the forelimbs. Histologic study showed involvement of both columns of Burdach at the same level. The degeneration of these columns could be traced to their termination in the nuclei of Burdach proper and the nuclei of Clarke and Monakow. Below the lesion there was no evidence of degeneration of the pyramidal tracts.

In a third monkey, section of the dorsal columns was performed at approximately the seventh thoracic segment. One week after operation the animal was able to walk with ataxia and showed deficiency of spontaneous grasping movements. The deep reflexes were active. There was hypotonia with no sensory changes. The hopping and placing reflexes and the sense of position of the limbs were lost. All these findings were confined to the hindlimbs. Two weeks after operation the findings were essentially the same, though present to a lesser degree. The involvement following the lesion in the region of the seventh thoracic segment is not as marked as that following the lesion in the columns of Burdach. Histologic studies showed the lesion to be between the seventh and the eighth thoracic segment, involving the dorsal aspects of the cord and extending slightly into the gray matter to involve some of the cells of Clarke's column. This produced some ascending degeneration in the dorsal spinocerebellar tracts, which were not directly involved by the lesion. There was no degeneration of the pyramidal tract. The degeneration of the dorsal column could be traced upward to the termination of the nuclei in the medulla.

The complex symptomatology presented by these animals appears to be dependent mainly on involvement of the sense of position or movement, or of a sense which

enables the animal to appreciate postures of the limbs and continuity of movement. Ferraro and Barrera were able to confirm the existence of three main cellular groups in the terminal nuclei of the dorsal column in the medulla. The first two groups are the well recognized nuclei of Goll and Burdach. The third group of cells has been variously described as the nucleus of Monakow, the nucleus corporis restiformis, etc. The authors prefer to call it the nucleus of Clarke and Monakow, in favor of Clarke, who first described it, and Monakow, who first established its cerebellar connections. Ferraro and Barrera found that the columns of Burdach send a large portion of their fibers to the nucelus of Clarke and Monakow in addition to fibers which terminate in the nucleus of Burdach, thus establishing a cerebellar component of afferent fibers from the upper extremities. Thus, the additional involvement of the cerebellar component in lesions at the cervical level is not met with in lesions of the posterior column of the spinal cord in the lower portion of the dorsal, the lumbar or the sacral region, where the cerebellar component travels in the main in the spinocerebellar tracts. The loss of two main afferent components in lesions at the cervical level is associated with greater involvement of the upper limbs as compared with the lower limbs. Ferraro and Barrera, using gross methods of testing, found that sensation of pain and diffuse touch appeared to be intact in the experimental animal. SALL, Philadelphia.

RESEARCHES ON FOCAL INFECTION: THE PROBLEM OF ELECTIVE NEUROTROPISM OF THE STREPTOCOCCI. V. CHINI and F. CORELLI, Riv. di neurol. **8**:1 (Feb.) 1935.

In continuation of previous work relating to the subject of elective organotropism of the streptococci, Chini and Corelli investigated the problem of neurotropism. The results were compared with those obtained by Rosenow and in general did not confirm his results. Experimental work was done by the intravenous inoculation of rabbits with cultures of streptococci obtained from focal infections of subjects with neuritis, chorea and other diseases of the nervous system. These injections produced in only a small number of animals the appearance of lesions in the nervous system of either the peripheral or the central type. There was a slightly higher percentage of animals with manifestations of lesions of the nervous system in this experimental group, but the difference between this higher percentage and the slightly lower percentage obtained in other groups studied was not considered sufficient to justify the formulation of a law.

Chini and Corelli do not think that their results confirm the existence of neurotropism. This tropism does not appear to be specific, constant or elective in the strict sense of the term. From their observations they decided that it was not possible to interpret either the etiology or the pathogenesis of the disease.

BARRERA, New York.

CONSIDERATIONS ON THE GENESIS OF EXPERIMENTAL INTERNAL HYDROCEPHALUS PRODUCED BY LAMPBLACK. P. REDAELLI and A. PREVITERA, Riv. di pat. nerv. **44**:601 (Nov.-Dec.) 1934.

Redaelli and Previtera studied the production of internal hydrocephalus in newborn cats by the injection of lampblack into the cerebellar system. They think that there is a temporary but slight hypersecretion of cerebrospinal fluid due to the mechanical disturbances produced by the operation. They also believe that lampblack may produce a temporary hypersecretion of liquid by irritation. Later, as a result of the irritant action of the lampblack, a foreign body granuloma is produced in the posterior tela chorioidea, the choroid plexus of the fourth ventricle and the surrounding meninges, causing an obliteration of the communication between the ventricular cavities and the subarachnoid space. As a result of such blockage there follows internal hydrocephalus. Later, because of the abnormal pressure of the increased amount of fluid, the vascular system of the choroid plexus may

be abnormally stimulated, and hypersecretion of fluid may be added to the mechanism of retention. Retention, though it is an important factor, cannot be considered the only one in the pathogenesis of internal hydrocephalus.

FERRARO, N. Y.

CHANGES IN THE NERVOUS SYSTEM CAUSED BY EXPERIMENTALLY PRODUCED SERUM ANAPHYLAXIS. A. STIEF and L. TOKAY, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:715 (Aug.) 1934.

The studies reported in this article are based on the observations on nine animals (guinea-pigs, dogs and rabbits). Guinea-pigs were the easiest to sensitize and dogs, the most difficult. Clinically, besides the vegetative disturbances, the motor symptoms, such as paresis and epileptiform, clonic and tonic seizures, and changes in postural reflexes were most striking. The histologic changes varied with the intensity of sensitization and the appearance of different symptoms in the animals. Ventricular and subarachnoid hemorrhages occurred in guinea-pigs, and hemorrhages in the parenchyma of the brain were more characteristic for dogs. The changes in the nerve cells showed transitions from so-called ischemia to severe cellular disturbances (acute liquefaction, granular decay, dissolution of Nissl substance, homogeneity of the protoplasm and dark pointed nuclei).

MICHAELS, Boston.

EXPERIMENTAL STUDIES OF THE INFLUENCE OF ROENTGEN RAYS ON THE MATURE BRAIN. W. SCHOLZ, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:765 (Aug.) 1934.

Demonstrable changes in the brain can be observed when the skulls of adult dogs are exposed to specified doses of roentgen rays. Early reactions and late damage must be differentiated. The early reactions consist of inflammation-like changes in the meninges and in the blood vessels. These are produced in the dog with 4 unit skin doses (as used in man) at one exposure. They attain their complete development five or six weeks later. The later injuries do not occur before from three to six months. They consist of multiple, localized areas of necrosis and hemorrhages in the white matter. Chronic progressive changes in many small blood vessels and capillaries of the nature of fibrosis, hyalinization and endarteritis follow. A direct injury of the nerve parenchyma by the irradiation is not anatomically demonstrable.

MICHAELS, Boston.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

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C. Burns Craig, M.D., *Chairman*

Xanthomatosis and the Syndrome of Diabetic Exophthalmic Dysostosis. Dr. S. Bernard Wortis, Dr. Abner Wolf and Dr. Cornelius G. Dyke, New York.

The syndrome of defects in the membrane bones, exophthalmos and diabetes insipidus has been recognized as a systemic manifestation of disturbed lipoid metabolism. This symptom complex was first described in 1893, by Hand, who considered the disease to be a tuberculous granuloma of bones associated with dyspituitarism due to secondary hypophyseal involvement. In Hand's case a soft yellow (xanthomatous) area about 1 inch (2.5 cm.) in diameter involved the entire thickness of the right parietal bone. In 1916 Schüller, of Vienna, reported two additional cases in which the characteristic roentgenographic picture of the skull was noted, and in 1919 Christian described another case. Both Schüller and Christian believed that the entire clinical picture is due to dyspituitarism. In 1925 Thompson, Keegan and Dunn reported a case with complete postmortem observations. In 1928 Rowland reviewed these cases and the related literature, described two new cases of his own and formulated the idea that Hand-Schüller-Christian's disease is a form of xanthomatosis due to a disturbance in lipoid (cholesterol) metabolism. Up to this time only fifty-seven cases of xanthomatosis of Hand-Schüller-Christian's type have been reported in the literature.

The etiology of xanthomatosis is not known. It is doubtful whether trauma or infection plays any rôle in its occurrence. Rowland and L. Pick expressed the opinion that there is an underlying congenital disturbance in the lipoid metabolism. The onset is usually insidious. It may occur at any age but has a special predilection for young boys. There may be soreness of the head and of the mouth; the teeth may fall out, and generalized maculopapulopustular hemorrhagic lesions of the skin commonly coexist. These "eczematous" manifestations are produced by accumulations of lipoid in the skin and are especially resistant to treatment. Later, anemia, exophthalmos, polydipsia and polyuria supervene. The disease may progress until the lungs become involved with secondary fibrosis, producing dyspnea and cyanosis. The liver and spleen may become enlarged. The long bones, membrane bones, dura mater, hypophysis, orbits, skin, lungs, heart, liver, spleen, pancreas and lymph nodes may be involved by the lipoid-laden histiocytes.

Epstein and Lorenz showed that there is a tendency for specific lipoids to be deposited in the different varieties of xanthomatosis. In Hand-Schüller-Christian's disease the lesions contain considerable cholesterol. This is confirmed by the work of Cowie and Magee. There is apparently a significant increase of cholesterol content only in the xanthomatous masses. The other body tissues have a normal lipoid content. In Gaucher's disease there appears to be an increase in the amount of cerebrosides, especially kerasin. In Niemann-Pick's and Tay-Sachs' diseases there is a selective increase in the phosphatides in the brain, mainly in the lecithin.

The studies of the cholesterol content of the blood made so far in cases of Hand-Schüller-Christian's disease have not shown any characteristic aberration. Normal values were obtained in two of our cases. In the third case no analysis of the blood for cholesterol was made.

Three cases of xanthomatosis observed in the Neurological Institute of New York in the past year are described.

DISCUSSION

DR. CHARLES DAVISON: The speakers have so ably covered the subject that I have little to add. They stated that the cholesterol content of the blood was normal in their cases. I wish to ask what the percentage of the total fat content of the blod was. In the case I reported the cholesterol content was normal while the total fat content was high. In a number of other cases reported in the literature similar findings were recorded.

In my case of xanthomatosis I looked carefully for xanthoma cells in the central nervous system. They were found in the capsule of the pituitary gland, but in the central nervous system I found areas of demyelinization filled with collections of giant glia cells and compound granular corpuscles. Because of these changes I concluded that the giant glia cells were part of a gliotic process and were similar in this respect to the fibroblasts in the fibrotic areas of other organs. The compound granular corpuscles, derivatives of the microglia cells, which in turn are part of the reticulo-endothelial system, were considered at the time to be analogous to foam cells. At the time the report of my case was published, Chiari, of Vienna, reported a case of xanthomatosis and luckily succeeded in demonstrating foam cells in the central nervous sysem. Stimulated by his observations, I made further sections and found a few collections of foam cells. The first section showed the typical foam cells in the capsule of the pituitary gland. The second showed the plaques of demyelinization. In the next there were collections of large glia cells and compound granular corpuscles. The last section showed small collections of foam cells in the low and high power magnifications. These and Chiari's findings illustrate that xanthoma cells may also occur in the nervous system.

DR. THOMAS K. DAVIS: I wish to congratulate the readers of the paper on their description of xanthomatosis; they have presented a great deal of material. The true source of the condition is still unknown. It seems to me to be a condition in which the disturbance of the fat embolism is in juxtaposition with the phagocytic activity of the typical cell of the reticulo-endothelial system, the histiocyte. When these changed cells accumulate in the skin, the resulting formation is known as a xanthoma. I wonder, therefore, whether one is not justified in using the term lipohistiocytosis for the process in other parts of the body rather than xanthomatosis, which is related to the skin.

The condition has too many proper names. I have the impression that the presenters feel the same way and are inclined to get away from the use of them. Whether Gaucher's disease, Niemann-Pick's disease and Schüller-Christian's disease are separate entities will not be decided until one can say with certainty whether they arise from different types of disturbance of the fat metabolism or whether the differences are due to different sites in which there is a secondary phagocytic histiocytic reaction.

DR. BERNARD SACHS: I had the opportunity of reading this paper before it was presented. It describes a rare disease, and I think that a great deal may be gained from further study of the cases presented. I have been interested not only in these cases, which I happened to observe lately at the Neurological Institute, but also in a case which Dr. Hausman reported to me for discussion at least four years ago. As far as the question of nomenclature is concerned, I discussed it with him and concluded that the best thing to do in finding the proper designation for the disease was to find out its main features. We agreed that diabetic exophthalmic dysostosis was the best possible term. The point that interests me particularly, however, in this case is the knowledge gained during the past few years of the importance of general lipoid metabolism and of the disorders of lipoid metabolism throughout the system. The cases reported have brought up the analogy between the symptoms presented and those seen in cases of Niemann-

Pick's disease and of amaurotic idiocy. A marked disorder of lipoid metabolism is seen in many cases of these conditions, and is, I think, the feature of most significance. However, there is another point that interests me, which I think is really the most striking of all; that is, how is one to account for disorders of lipoid metabolism as a familial disease? I have had the suspicion that there may be some factor which accounts for this, and I believe that a thorough examination of the entire endocrine system will reveal evidence of great importance. I do not know if a complete autopsy has been made in any of these cases. I should be interested to know whether similar changes have been found in the liver and spleen and in other organs in which cellular changes at least have been found that were similar to cellular changes in the central nervous system. It is well to be on the watch for cases belonging to this entire group of diseases. They are evidently much more frequent than has been thought. The clinical picture and above all the roentgenographic picture of defects, especially that of the defects in the skull, are so marked that I think they will be recognized much more easily hereafter than in the past, but I should especially like to call attention to the importance of further and more accurate examinations of the endocrine system. Studies should also be made to find out what is basically wrong with the lipoid metabolism and, if possible, to determine how that defect in lipoid metabolism is brought about.

Dr. S. Bernard Wortis: I agree with Dr. Sachs, Dr. Davis and Dr. Davison that the terminology of this disease will probably undergo a change in the next few years. The xanthomatoses will probably be named on the basis of the disturbance in metabolism of the specific lipoid. The cholesterol metabolism is suspected to be at fault in Hand-Schüller-Christian's disease. Phosphatide metabolism is at fault in Niemann-Pick's and in Tay-Sachs' disease. Xanthomatosis was noted in almost all organs in the case reported by Thompson, Keegan and Dunn and in the one described by Wheeler a number of years ago. It is worth noting at this time that a great amount of knowledge has been gained concerning the rôle of different substances in body metabolism. For instance, cholesterol is related to vitamins A and D and to the so-called carcinogenic substances. The amount of the phosphatides is increased or diminished in certain diseases. For instance, dementia paralytica is associated with the loss of large quantities of phosphatides from the brain tissue. I believe that one may be able to solve some of the problems of nervous and mental disease along these neurochemical avenues of research. In answer to Dr. Davison, we did not determine the total fat content in our cases.

Intracranial Tumors: Report of Two Cases in Which Complete Removal Was Done, with Recovery. Dr. Abraham Kaplan, New York.

In the first case is presented a large neoplasm which failed to give any localizing signs and which was unexpectedly found on roentgenographic examination of the skull. In the second is presented an unusual complete enucleation of a midline cerebellar medulloblastoma.

Case 1.—L. S., aged 35, was admitted to the neurologic service of the Bellevue Hospital on May 5, 1934, because of failing vision for the past six months. She had been married for twelve years and had three children who were living and well. Appendectomy was performed five years before. The onset of the illness took place five years previously, with headaches in the parietal and occipital regions, which were made worse by bending or straining. The headaches became progressively worse until five months before entry, when the patient visited a sister in Baltimore, where an operation was performed on one of the sinuses, with some relief in the severity of the headache. There was no associated nausea or vomiting. Six months before her entry to the Bellevue Hospital vision began to fail; objects became dim and blurred, and soon the patient could distinguish only large print. There was no diplopia. For two months memory for recent events had been faulty. There were also transient numbness, paresthesia and intermittent pains in the arms and legs. There were no convulsions, paresis or tinnitus.

The patient was moderately obese, with a habitus suggestive of a dysfunction of the pituitary gland. There was no tenderness of the skull, and the pupils were equal and regular and reacted promptly to light and in accommodation. The ocular fundi showed bilateral papilledema of 3 diopters. The vessels were markedly full and tortuous, but there was no evidence of hemorrhage or exudate. Visual acuity was 20/100 in the right eye and 20/60 in the left, and the fields showed concentric contraction. There were no other abnormal neurologic signs.

Examinations of the blood and urine gave normal results. The blood pressure was 130 systolic and 80 diastolic. Examination of the spinal fluid showed a pressure of 360 mm., absence of cells, a total protein content of 70 mg. per hundred cubic centimeters and a negative Wassermann reaction. Roentgenograms showed an irregular area of calcification, 3 by 4 cm., in the right precentral region close to the midline.

On March 23 craniotomy was performed in the right frontotemporal region and was attended by considerable bleeding. No attempt was made to remove the tumor.

On April 17 the wound was reopened. As the dura was reflected toward the midline, the surface projection of the tumor came into view. This was about the size of a quarter. By gentle manipulation it was possible to shell out completely the entire tumor, which was attached to the sagittal sinus. It was irregular in shape, measured 6 by 6.5 by 5 cm. and weighed 98.5 Gm. Histologically, it was a typical meningioma.

The postoperative course was smooth, and the patient was discharged on May 5. Since then she has been free from headaches and is now able to carry on household duties as usual.

CASE 2.—G. B., a Negro servant, aged 22, was admitted to the neurologic service of the Bellevue Hospital on April 23, 1934, complaining of headache and vomiting of two months' duration. She had had measles and whooping cough in childhood. The marital and the family history had no bearing on the illness. She had been well until two months before admission, when she was seized with sudden attacks of pain in the suboccipital region, which radiated to the vertex. The attacks recurred for a week with increasing frequency and then slowly subsided. The pain was very sharp and usually lasted from one to two hours. She also noted that straining or a sudden change of position aggravated the symptoms. One month after the onset of the headaches, nausea and vomiting set in and were followed shortly thereafter by spells of dizziness and unsteadiness, so that on several occasions the patient was mistaken for being drunk. She had to remain in bed. For six weeks she noted gradual impairment of vision but no diplopia. She had lost 25 pounds (11.3 Kg.) since the onset of the illness.

The patient was acutely ill but was alert and cooperated admirably in the examination. The pupils were slightly dilated but reacted promptly to light and in accommodation. There was only slight horizontal nystagmus and no limitation in the upward gaze. Both ocular fundi showed acute papilledema with many flame-shaped hemorrhages and exudate. Visual acuity was 20/70 in the right eye and 20/60 in the left; the fields showed concentric contraction, with enlarged blindspots. There was a suggestion of Romberg's sign with a swaying to the right, but when the finger-to-nose test was performed with the right hand only slight ataxia was elicited.

The urine showed no abnormality. The blood pressure was 95 systolic and 80 diastolic. The Wassermann reaction of the blood was negative. The nonprotein nitrogen content was 33 mg. per hundred cubic centimeters, and the sugar content, 84 mg. Roentgenograms of the skull showed increased pressure markings and slight separation of the coronal suture. Because of the high degree of papilledema, spinal puncture was not done.

A diagnosis of a neoplasm of the posterior fossa in the midline was made. It was suggested that a possible diagnosis of a tumor of the third ventricle be ruled out.

Ventriculography was performed on April 8. Films taken after the ventricular fluid was replaced by air showed dilatation of both lateral ventricles and a well outlined and dilated third ventricle. The air seemed to end abruptly at the posterior portion of the aqueduct.

On May 21, with the patient under anesthesia induced with tri-bromethanol in amylene hydrate, a craniotomy was performed in the suboccipital region. As the vermis was incised a grayish yellow tumor came into view, which fortunately shelled out completely. It was round and regular and measured 4 by 3 cm., having a projection at one end which had occupied the posterior portion of the aqueduct.

The report on the microscopic studies of the tumor by Dr. Lewis Stevenson follows: "The slide shows a very cellular tumor consisting of closely packed nuclei with scanty cytoplasm and a rather frail connective tissue stroma. The nuclei under high power are round to oval, varying considerably in size and containing abundant chromatin. In several places the nuclei arrange themselves about a hollow space, forming what is termed 'pseudorosettes.' There are numerous mitotic figures scattered throughout. The pathologic diagnosis is medulloblastoma."

The postoperative course was satisfactory. Roentgen therapy was given to the suboccipital region, the entire spine and the area of both lateral ventricles. By the third postoperative week the patient was out of bed and was able to walk; shortly thereafter she left the hospital in excellent condition. It is now eleven months since the operation, and there is no evidence of recurrence.

ONE HUNDRED CONSECUTIVE OPERATIONS FOR TRIGEMINAL NEURALGIA IN PATIENTS FROM SIXTY TO EIGHTY YEARS OF AGE. DR. BYRON STOOKEY, New York.

THE USE OF TRI-BROMETHANOL IN AMYLENE HYDRATE AS ANESTHETIC FOR ENCEPHALOGRAPHY. DR. JOHN E. SCARFF, New York.

In an effort to minimize the pain incident to encephalography I have recently employed tri-bromethanol in amylene hydrate for anesthesia with most gratifying results. A preliminary report of twenty-five cases is here made. None of the patients had increased intracranial pressure or a neoplasm of the posterior fossa. Small preliminary doses of morphine and ephedrine were given; a dose of tri-bromethanol in amylene hydrate containing 90 mg. of tri-bromethanol per kilogram of body weight was first given, with an additional 10 or 20 mg. if necessary to produce satisfactory anesthesia. There were no undesirable reactions of any consequence. The patients slept peacefully during the procedure and for some time afterward. The signs of shock which usually accompany encephalography were noticeably absent.

A simple mechanical frame devised by me has greatly simplified the management of the unconscious patients. The frame is made of metal and canvas and is placed directly on top of an ordinary hospital stretcher. Its essential feature are two hinged leaves by means of which either end of the frame can be elevated. With these the patient can easily be supported in any desired position. As a matter of practice the patient is usually placed first in a lateral reclining position, then in an upright position and, finally, in the opposite lateral reclining position. This permits thorough emptying of all parts of the ventricular and cerebral subarachnoid systems and, corresponding to this, complete filling of these spaces with air.

For routine work I have found that when the ventricles and arachnoid spaces are thoroughly filled with air, roentgenograms taken with the patient in the horizontal prone position alone are sufficient for most diagnostic needs. Occasionally, for additional information, roentgenograms taken with the patient in the upright position may be desirable. In such cases the frame is of great assistance in supporting the patient while the exposures are being made.

DISCUSSION

DR. LEO DAVIDOFF: Dr. Scarff has undoubtedly presented a stimulating point of view. Much is to be said in favor of relieving patients of the pain incident to encephalography. However, the pain depends on a number of factors, perhaps the most important being the quantity of air injected. It has been the experience of myself and my colleagues in over two thousand encephalographies performed at the Neurological Institute that pain seldom, if ever, arises from the injection of the first 25 to 30 cc. of air. It begins when 30 or 35 cc. of air has been injected. The roentgenogram taken after this first injection of air tells approximately how much air should be used. I think that the average amount for ventricles of normal size is less than Dr. Scarff uses. I use from 50 to 70 cc., perhaps. The result is that though the patient does experience headache, the duration of the discomfort is much diminished. We have also found that the number of patients whose ventricles do not fill with air is definitely greater when general anesthesia is used than when local anesthesia is employed. Of course, we always use general anesthesia for children. We have found that the number of children whose ventricles do not fill with air is also definitely greater than the number of adults. When we tried to check the cause for this, we found that one of the things the children have in common with adults whose ventricles do not fill with air is the fact that general anesthesia is used. I wish to ask Dr. Scarff, therefore, in how many patients who were anesthetized with tri-bromethanol in amylene hydrate he has failed to find filling of the ventricles with air. I was also much interested in Dr. Scarff's films taken with the patient in the horizontal position. I wonder if he has checked the roentgenograms made in those cases in which he believes he has drained the ventricles thoroughly with roentgenograms made with the patient in the upright position. As I recall from our own pictures, taken without manipulation of the head and with the temporal horn turned uppermost, the pictures made with the patient in the horizontal position look exactly like those which Dr. Scarff has shown; yet in our cases the pictures made with the patient in the upright position fail to show the temporal horn. There are certain things that are brought out by studies made with the patient in the upright position that do not appear in views made with the patient in the horizontal position. The positions Dr. Scarff describes for emptying the ventricles seem logical to me. If he can show me that by their use the temporal horns will also be visualized in the views taken with the patient in the upright position, I shall be much interested to try them.

DR. CORNELIUS G. DYKE: I think that Dr. Scarff's apparatus is ingenious and certainly seems of value in handling the anesthetized patient. Dr. Davidoff has expressed an opinion on this matter similar to my own. I believe that much of the discomfort caused during and after the procedure may be eliminated by injecting a minimum amount of air. In the average case this is about from 50 to 70 cc.

One objection to using a general anesthetic is that the cooperation of the patient cannot be utilized during the taking of the films. This often results in roentgenograms which are blurred because of motion of the head during respiration. Furthermore, it is my experience that the use of general anesthesia increases the number of cases in which the ventricular system is unsatisfactorily visualized.

These two objections have led me to continue doing the procedure with the patient under local anesthesia.

DR. GEORGE H. HYSLOP: It is always the patient who knows how much a process hurts. Dr. Scarff described the suffering produced by this procedure as comparable to that caused by a major operation without anesthesia. I recall that Pepys, in his "Diary," described being "cut for the stone." It took a number of persons to hold him down. His position was similar to that of a man at the bottom of a pile of football players. I have never seen a patient acting as if there was any such degree of suffering while encephalography was being carried out.

There are two factors which do definitely influence the amount of suffering that is complained of by a patient. If he is in a ward, the degree of suffering often depends on what he has heard others say. The second factor is the preparation of the patient's mind by the physician for what is undoubtedly an uncomfortable procedure. One-quarter grain (16 mg.) of morphine is of no value to a patient who cannot stand much pain or discomfort. Such a patient should be anesthetized with tri-bromethanol in amylene hydrate. It not only prevents suffering but makes the procedure easier for the operator and the others concerned. There is no virtue in being sadistic, and one should avoid causing pain whenever possible. In my experience, the patient with a good morale is not going through such torture as Dr. Scarff described.

DR. RICHARD M. BRICKNER: Is there any reduction of the subsequent pain, that is, the pain occurring two or three days after encephalography, from this procedure? Is there any danger in moving a patient around so much while the lumbar puncture needle is in place?

DR. JAMES L. JOUGHIN: I have been much interested in this presentation by Dr. Scarff. He has stressed the points which seemed to be of the greatest value in this particular method. I have seen some patients, perhaps a small percentage, who seemed to have no reaction after encephalography, either at the time of the procedure or subsequently. Then I have seen, as have most physicians, the majority of such patients suffering rather severely and a smaller number suffering intensely. I believe that for the latter group this method is valuable. Dr. Scarff is presenting his material as a preliminary report, and obviously it is impossible to compare the results in a series of twenty-five encephalographies with results such as Dr. Davidoff and Dr. Dyke presented from the Neurological Institute. Excluding the mechanical phase, the great difference in the two procedures is that Dr. Scarff takes all the fluid out of the ventricles and the subarachnoid spaces and injects sufficient air to fill those spaces. That, of course, according to Dr. Davidoff and Dr. Dyke, is rather heretical. When they wrote their paper on encephalography, published in the *Bulletin of the Neurological Institute of New York* (**2**:331, 1932), they had an impression that the more air injected the more pain was likely to be caused, but I do not know whether this assumption has now become a conviction. While with this procedure the patient obviously does not suffer as the encephalography is being done, it would be interesting to know to what extent he suffers in the days following encephalography, considering that all the fluid has been replaced with air. If Dr. Dyke and Dr. Davidoff are correct in their view, one would expect considerable pain to result, but I do not think that Dr. Scarff's patients experienced this. I think that this procedure ought to be tried out where a greater number of encephalographies are performed in order that definite conclusions may be reached as to the value of the procedure. I should also like to know how many pictures Dr. Scarff finds it necessary to take.

DR. ISRAEL STRAUSS: Can Dr. Scarff, with the ordinary x-ray apparatus, take pictures with the patients in the upright position in the frame he has described?

DR. SCARFF: Dr. Strauss asked if this frame can be utilized for supporting patients in the upright or sitting position while roentgenograms are taken. I believe that it can be easily adapted to this use if desired.

Dr. Davidoff objected to the quantity of air that I have been using. He stated that in his experience the degree of pain had been found to be proportional to the amount of air injected. I am sure that that is true within certain limits. He stated also that the average patient experiences no pain until after 20 cc. has been injected. That also may be true. But, Dr. Davidoff uses approximately 75 cc., which by inference would be painful and which after all is not much less than the 90 cc. I use. I do not remove all the cerebrospinal fluid. I remove about 90 cc., which drains the ventricles and the intracranial subarachnoid spaces but not the spinal subarachnoid spaces. I use from 10 to 15 cc. more air than Dr. Davidoff and Dr. Dyke use.

Dr. Davidoff asked the number of cases in which air failed to enter the ventricles since I began the use of tri-bromethanol in amylene hydrate. I have had no such cases, and strangely enough before I used this type of anesthesia I had quite a number of cases in which air did not enter the ventricles, perhaps 10 per cent of my cases.

Dr. Brickner noticed in the photographs that the spinal puncture needle was not withdrawn until the various changes in posture had been made and asked why. The reason is this: After the first 5 cc. of spinal fluid has been withdrawn, 15 cc. of air is injected. This increases the internal pressure just enough to make the fluid flow out readily. After all the air is injected, the syringe is disconnected and the needle left open and in place, in order to allow the excess 10 cc. of air to escape. Since I have been employing this simple trick of over-injecting air at the start, I have had no failures in filling the ventricles with air.

Dr. Dyke thinks that roentgenograms taken with the patient in the upright position are a great help in revealing certain anomalies of the third ventricle and the basal cisterns. It has been the belief that if the ventricular and cerebral subarachnoid systems are completely filled, as with my method, instead of only partially filled, as with the old method, all the information necessary for a diagnosis can be obtained from the roentgenograms made with the patient in the horizontal position. The frame, however, is available for holding an unconscious patient upright while roentgenograms are made, if this is desired.

The severity of the pain which is produced by encephalography performed without anesthesia is something which I do not wish to discuss anew. I have stated my beliefs regarding the severity. I am aware that the reaction to pain is not the same in all patients, but I am sure that many patients suffer severely, and it is for this group that I have attempted to work out this procedure.

THE TREATMENT OF ABSCESS OF THE BRAIN ASSOCIATED WITH EXTRACAPSULAR NECROSIS AND SUPPURATION OF THE BRAIN. DR. JOSEPH E. J. KING, New York.

Experience gained in two cases of abscess of the brain with extracapsular necrosis and suppuration of the brain forms the basis of this paper. These are the only two cases of this type which have been observed by me. Both patients were operated on, and both recovered. In presenting this subject with the report of the cases, it is hoped that the information obtained from the observations made may be of help to others in dealing with similar cases.

I believe that if fairly wide open exposures were made, which allow proper inspection at operation, and if complete reports were made of autopsies, no doubt a coexisting noncommunicating extracapsular suppurative or necrotic process in the substance of the brain would be found in a number of cases. Considering the uneventful courses in the two cases presented in detail in this paper, it is believed that a number of such patients would recover if subjected to this type of operation.

Summary.—Detailed reports of the pathologic changes associated with abscess of the brain, including its variations noted at operation or autopsy, would improve knowledge of the subject and would help in determining the proper procedure to be used in a given case.

The actual condition at operation, especially the presence or absence of extracapsular suppuration and necrosis, can be ascertained better by the "open" method of dealing with the abscess than by the "closed" procedure. In some cases in which extracapsular infection is present and in which the operative method described is used there might be a better chance of recovery.

Two cases of abscess in which there were extracapsular necrosis and suppuration are reported. Both patients recovered.

The method of dealing with the capsule is described, and retention of the capsule or a part of it, if possible, is advocated.

Brief mention is made of the operation and results in two cases of metastatic abscess of the brain.

DISCUSSION

DR. WELLS P. EAGLETON: In 1912 I wrote a book on abscess of the brain, to which Dr. King has referred and about which he was complimentary (Brain Abscess, Its Surgical Pathology and Operative Treatment, New York, The Macmillan Company). An effort was made to put down in detail in this book what I had observed in a large number of cases of abscess of the brain. The results have been criticized, but the book has an advantage over other books in that it contains what I saw at the time of operation and what I had learned from my mistakes and experiences in the treatment of abscesses of the brain. It has had a remarkable effect all over the world. I have received letters from men in many different parts, saying: "I had a case just like your case no. so and so." Dr. King is doing the same thing; i. e., he is giving a detailed account of his results. Whether one is successful or not, an extensive report of the results is the only way to help others to learn. The results of treatment of abscess of the brain in my hands have been very poor. I think that if one obtains recovery in 25 per cent of cases of abscess of the temporosphenoid region, in about 50 per cent of cases of cerebellar abscess and in 75 per cent of cases of abscess of the frontal lobe, one is doing well, but I have learned that the patients who get well are those who have an encapsulated abscess.

I have come to this understanding: There may be an abscess in the brain for a long time without any definite symptoms arising. In the last case of which Dr. King spoke the patient had pain for seventeen years or more. Numerous operations were performed on his nose and accessory sinuses with the hope of relieving the pain in his head. If a man has a pain in his head, one will never relieve it by operating on the sinuses. There are a few things that apparently were not done in these cases. First, no repeated systematic examination was made of the vestibular apparatus. If a man has increased intracranial pressure, every one examines the eyes. If he has papilledema, one knows that he has increased intracranial pressure. In a case of increased intracranial pressure, even without papilledema, if one syringes the ear with cold water with the patient in the upright position, there may be no nystagmus. If the patient is placed in the horizontal position and the test carried out, he has marked nystagmus. I call this the vestibular sign of increased intracranial pressure. I discovered it a great many years ago. I do not know why all neurologists do not use it. Years ago some one wrote a book about vertigo which was full of theoretical conceptions regarding vestibular tests, and this book tended to discredit them. But the vestibular sign of increased intracranial pressure is practical.

Why were not the visual fields measured repeatedly in the second case? When a patient has an abscess of the brain, there are times when the abscess swells a little. At such times there is an indentation of the visual field. The next day the edema may be gone. An abscess of the brain is an inflammatory process. When edema is absent the indentation is gone. I had a patient with an abscess of the brain for whom I recorded the visual fields sixty-five times. He learned that when the field "went in," I was going to do something about the abscess. These patients do not know that there is an indentation, but if a trained technician records the visual fields every day and the abscess is in the temporosphenoid lobe or even in the frontal lobe, the field will suddenly contract and then a diagnosis may be made.

Personally I think one should treat an abscess of the brain as one treats an abscess in any other part of the body. There is a popular belief that one should make a small opening and put a small drain in it. The few patients with abscess of the temporosphenoid lobe in the substance of the brain itself that I have operated on have recovered because I made a large opening and tried treating them as I would if the pus were in some other location.

DR. LEO BUERGER: I think that I owe my life to Dr. King, Dr. Craig and their assistants and associates. The only thing I want to say is this: As far as the history goes, the headaches date back over forty years. There was persistence of headaches, and there was never a moment during the forty years when I was

free from them. The diagnosis was made five or six months before the operation was performed. The condition was easy to diagnose. Dr. Craig did urge me for a long time to have something done, not because of the abscess but because of the danger of infection by way of the tract which led upward along the orbit from the para-orbital cell.

Recovery was uneventful. There was no suffering during the operation (with anesthesia induced by tri-bromethanol in amylene hydrate) or afterward, except for the mental anguish occasioned at one time by the thought that the infection might spread into the ventricles.

Another point worthy of note by those diagnostically minded was that a diagnosis of neurasthenia and neuralgia was frequently made in my case. I was always convinced however, that the pain was due to a pathologic process in my sinuses and basal plate. Since the operation, my only symptoms have been attacks of vertigo; they are diminishing and have been successfully treated by Dr. Craig by inflation of the eustachian tube; also there is diplopia, which is a little more distressing now than after the first operation, performed in 1918.

Dr. S. Bernard Wortis: I saw Dr. King's first patient, and I think that he is to be congratulated on the great amount of courage he exhibited in removing large amounts of necrotic brain tissue. Careful studies of the visual fields were made on both his patients, and one was operated on because she had a progressive quadrantal hemianopic defect, which developed in association with anomia.

Dr. King has received much too little credit for the procedure that he developed for the surgical treatment of abscess of the brain. Radical surgical measures are usually necessary, and Dr. King was the first person to attempt such treatment. His results, especially in the cases of severe involvement, have been remarkably good. I believe, as he does, that one must suit the surgical procedure to the particular case.

Dr. Israel Strauss: First, I want to compliment Dr. King on his results. In fact, I know the patient in the first case he reported. The only service rendered in that case was that he urged that the presence of bacteria in the smears of the spinal fluid, which was supposed to be indicative of meningitis, be disregarded, as that condition was not present. The second case illustrates what a clever craftsman can do, and removal of an abscess of the brain requires real craftsmanship. It is foolish for any one to say that the patient in this case had the abscess for forty years. He did not have it for seventeen years. I know something about abscesses of the brain and their capsules. The unfortunate thing is that I told the patient long ago that if the upper cell was not taken care of he would sooner or later have an abscess of the brain or meningitis. He said he did not know any one whom he would trust to operate in that region. He did not have anything done at that time, and he is fortunate to have been treated by Dr. King.

I wish to ask Dr. King a question in regard to the first case. The second one was definite enough. Pus was discovered after the injection of air. The patient diagnosed the first abscess himself by the use of a probe, and the second abscess was made evident by injection of air. That is easy. When pus was seen on the probe, it was evident that there was pus in the temporosphenoid lobe. In the first case reported, what led Dr. King to go through brain that was merely a little softened and reddened? Of course, every brain surgeon tries to wait for encapsulation of an abscess if he can, and he then uses the method of treatment that he prefers, for instance, the herniation method, which Dr. King has so ably used and described. What prompted Dr. King to remove the brain tissue by suction until the encapsulated abscess was reached? How did he know there was an encapsulated abscess? He knew pus was draining down into the mastoid wound, and he knew the long duration of the illness. He did not put a probe into the abscess. He did not know how encapsulated it was, except that from the history it had been present for at least from six to seven weeks.

Dr. Joseph E. J. King: Dr. Eagleton, who has had an enormous experience, spoke about the absence of examination of the visual fields in the two cases. Determinations of the visual fields were made in the first case and roughly in the second case. They were not necessary in the second case owing to the fact that the diagnosis was made before I was called. In Dr. Eagleton's book the mortality rate in cases of abscess of the brain is recorded as higher than 25 per cent, as he said, but I daresay that if one considered all abscesses of the brain together with all the complications as one meets with them (for example, rupture into the ventricles), no doubt the rate of recovery would be no more than 50 per cent.

Dr. Wortis was an important helper in the first case. This case was probably not one of true meningitis, in that the cell count in the spinal fluid never was as high as that found in cases of real meningitis, and although on one examination organisms thought to be streptococci were seen in the smear no growth was obtained. Therefore, from examination of the cerebrospinal fluid this was not a case of true meningitis. Dr. Wortis did a great deal of work on the patient before she came to operation.

Dr. Stookey spoke of the nonencapsulated abscesses. The third patient operated on by me, who is living and well, was a fireman. Operation revealed a considerable amount of broken-down necrotic brain substance with supernatant thin pus over detritus and a very faint capsule, which offered slight resistance to the cannula. The remainder of the abscesses, with two exceptions, were encapsulated.

In the two cases presented this evening there was definite encapsulation, but I could find no opening leading from the abscess cavity into the necrotic brain substance and pus.

One patient, who was operated on last year, was a surgeon, and the operation was performed on about the sixth day following the initial involvement of the brain secondary to a suppurative process in the lung. I performed the operation on the insistence of Dr. Kennedy, although we knew that definite encapsulation had not taken place. This patient was all right on Sunday, except that he had a cold in the head and was coughing. On Sunday night he had a violent intracranial episode. His temperature varied from 104 to 105 F., but by Thursday it was about 101 F. He had complete right hemiplegia, homonymous hemianopia, complete right hemianesthesia and motor aphasia. After reading the papers by Grant and others, we naturally desired to wait until a capsule had formed, but Dr. Kennedy thought that the patient should be operated on, as otherwise he might not survive sufficiently long for a capsule to form.

We made a small opening in the bone in the midmotor area and met with no resistance on puncture. Some rather dirty, dark material escaped along the cannula as it was moved about in a circular manner. I did a procedure somewhat similar to that done in the first case described. An opening about 2 inches (5 cm.) in diameter was made in the bone, with a corresponding smaller opening in the dura, which was fixed to the cortex. After removal of the cortex by suction, broken-down necrotic material and yellow pus were encountered. No growth was obtained from culture of this pus. A considerable amount of yellow necrotic brain substance was removed. The excavation was somewhat the shape of a fat ink bottle, i. e., larger in the subcortical area than at the surface. Complete removal of the yellowish material was not done for fear of entering the ventricle. In the first case described all of the yellowish necrotic brain substance was removed so far as could be determined, and the surface of the brain which lined the excavation appeared to be normal. The wound in the case in question (that of the surgeon with the metastatic abscess) healed in forty-two days. Later I did a plastic procedure and excised the scar, and the patient is well today except that he has some anomia and a loss of position sense in the right hand. He is able to carry on a conversation well; the hemiplegia, hemianesthesia and hemianopia disappeared, and he is able to use the right arm if he watches what he is doing with it. He makes false motions with it when his eyes are closed; i. e., there is loss of position sense.

This is the first patient with an actual metastatic abscess of the brain or suppurative encephalitis on whom I have operated.

There is a patient in the Bellevue Hospital who had a condition similar to the one described and was similarly treated. The only complication is that the patient tore his dressing off and infected the hernia.

It is believed that in these cases if the subdural and subarachnoid spaces are sealed off well and if the ventricle is not entered, the substance of the brain itself will resist a considerable amount of infection.

In answer to Dr. Stookey's question about deep abscesses: No attempt at herniation is made. In such cases it would be absolutely useless. Should I be confronted with such a situation I would be satisfied to leave a searcher or a catheter in the abscess as in the method advised by Dowman and Eagleton.

It is surprising to what degree the floor of an abscess will herniate to the surface. In one case the abscess cavity held nearly 7 ounces (210 cc.) of saline solution after it had been opened and washed out. In another case the floor of the abscess was about 3 inches (7.5 cm.) from the cortex. In my paper I discussed control of herniation, but time would not allow me to read that portion. At present I control herniation if necessary by lumbar puncture, which can safely be done after seven or eight days. The excessive herniation allowed and advocated in my original paper is not permitted now. As soon as the floor of the abscess is on a level with the dura, so that a secondary pocket cannot form, herniation has advanced sufficiently far and should be controlled. By controlling it, possible leakage from the ventricle will be lessened.

Dr. Strauss stated that in the second case the patient did not have an abscess for forty years. I do not think so either. Just how long the anterior abscess had been present none of us could state. He also asked how we knew that pus was present in the first case. As already stated, this was determined by aspiration of thick greenish-yellow pus through the cannula.

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ABSTRACTED BY WALTER FREEMAN, M.D., Washington, D. C.

BLOODY TEARS AND EPILEPSY. PIERRE BÉHAGUE.

A cavalry officer suffered an injury to the head, after which he had severe headache; later epileptiform seizures appeared, and the patient did not regain consciousness until there had been a caruncular hemorrhage, of about a thimbleful of blood, lasting three or four minutes and spattering over the patient's face. There was no doubt as to the nature of the fluid: Red blood cells could be seen under the microscope, and a Wassermann test was made. The cerebrospinal fluid was normal and did not contain blood. Neurologic examination gave negative results except for tremor of the hands.

Béhague stated that subconjunctival hemorrhages are not uncommon in cases of epilepsy and raised the question whether bleeding from the caruncle might be related to subconjunctival hemorrhages. Fribourg-Blanc stated that the two phenomena proceed from the same mechanism.

POSTROTATORY THRUST OF THE BODY AND COUNTER-ROTATION OF THE EYES. J. A. BARRÉ.

In several cases of otitis media in which there had been extensive destruction and degeneration in the middle ear, the inner ear was also affected, and normal

responses from rotation were not obtained. It seems probable that there was some involvement of the internal ear in these cases, and the author expressed the belief that the lack of responses cannot always be regarded as a positive sign of intrinsic disturbance of the inner ear.

ACUTE AND REGRESSIVE SYMPTOMS OF METASTATIC TUMORS OF THE BRAIN. RAYMOND GARCIN AND RENÉ HUGUENIN.

A metastatic tumor of the brain frequently gives rise to an acute onset of symptoms, followed by a temporary regression so regular and so complete that one is tempted to think of meningo-encephalitis or cerebral thrombosis.

A patient, aged 55, was first seen in May 1932 on account of right hemiplegia with aphasia of three weeks' duration which had developed in a few days. There was no indication of syphilis or hypertension; the fundi oculorum were normal, and roentgenograms of the skull showed no abnormalities. The spinal fluid was under normal pressure, and examination of the content gave normal results. Two days after lumbar puncture the patient went into coma, but he recovered; three months later there was nearly complete restoration to normal. The patient lost weight, however, and had a cough, but there were no tubercle bacilli in the sputum. Roentgen examination of the lungs showed a large mass, obviously a primary growth. In September intracranial hypertension appeared and progressed rapidly; death occurred in October, following signs of tremendous intracranial hypertension, paralysis and choking of the disks.

Garcin and Huguenin stated that the condition could probably be explained by embolism due to deposition of small clumps of cells from the primary growth in one of the end-arteries of the brain and producing acute but transitory symptoms.

THOMSEN'S DISEASE AND MYXEDEMA OF SIMULTANEOUS ONSET AND PARALLEL EVOLUTION. RAYMOND GARCIN, L. ROUQUES, LAUDAT and FRUMUSAN.

The association of progressive myopathy with glandular disturbances has been reported from time to time. No definite etiologic connection between these two conditions has been established, although the occurrence of tetany and its similarity to myotonia has suggested a parathyroid etiology.

In a man, aged 25, who had been an athlete, sluggishness and rigidity developed gradually at about the same time. There were well marked characteristics of myotonia, with a basal metabolic rate of —33 per cent, cold skin, dry hair, puffy face, hypertrophy of certain muscles and all the classic signs of both myotonia and myxedema. Chemical examination of the blood showed a slight deficiency of protein, with a high albumin-globulin quotient, and a rather high cholesterol content. Thorough study of myographic tracings and determinations of chronaxia revealed a slight increase in the chronaxia, though it did not approach that found in cases of true myotonia. The patient died of tuberculous bronchopneumonia. Necropsy showed extraordinary variability in the caliber of the muscle fibers, hypertrophy of the sarcolemma and a sclerotic appearance due to hyperplasia of the fields of Cohnheim. Histiocytes were noted in some of the muscle fibers. The thyroid gland was barely recognizable owing to intense sclerosis, cellular proliferation, degeneration of the acini and loss of colloid. The testes were atrophic and showed no spermatozoa. The hypophysis presented an adenoma of mixed acidophilic and basophilic type. The other organs revealed nothing of importance. The muscular condition and the myxedema were probably independent of each other, though occurring simultaneously, and were possibly due to some type of infection.

THE POSTERIOR ARACHNOID NETWORK IN SYRINGOMYELIA. T. ALAJOUANINE, T. HORNET, R. THUREL and R. ANDRÉ.

In operations for syringomyelia it is common to find the arachnoid thickened over the spinal cord. This observation led the authors to investigate the anatomic

picture in 6 cases of syringomyelia. It was found universally that over the syringomyelic portion there were considerable thickening and reduplication of the arachnoid network, which sometimes obliterated the subarachnoid space and sometimes extended the whole length of the spinal cord. The change was more marked in the thoracic region, and its location did not coincide with the site of syringomyelic changes.

The authors expressed the belief that this thickening of the arachnoid does not bear any cause or effect relationship to the cavitation in the spinal cord.

ACUTE MULTIPLE SCLEROSIS WITH SYMPTOMS OF NEUROMYELITIS OPTICA. T. ALAJOUANINE, T. HORNET, R. THUREL and R. ROSSANO.

A man, aged 33, who had tuberculosis experienced headache in the frontal region, associated with rapid loss of vision, leading in four days to complete blindness. This was followed by progressive loss of muscular power and hypotonia in the right arm and leg, exaggeration of reflexes, ankle clonus, an abnormal plantar reflex and loss of the cremasteric and abdominal reflexes. There were radicular hypesthesia along the inner border of the forearm and hypesthesia to pain and temperature in the left leg and, to a lesser degree, along the trunk. The pupils did not react to light but reacted in convergence. The spinal fluid was normal. Five weeks after the onset of the disorder the paralysis became almost complete in all four limbs, and the bladder became involved. Tubercle bacilli were found in the sputum. The patient died two months after the onset of the nervous condition. Postmortem examination revealed numerous foci of demyelinization. One area of demyelinization occupied the whole cross-section of the spinal cord; some foci had destroyed only the myelin sheaths; others affected the axis-cylinders, marked thickening of the perivascular spaces being present. A plaque of demyelinization occupied the central part of the medulla oblongata, and a considerable degree of reaction was present around the vessels everywhere. Moreover, there was well marked demyelinization in the subcortex throughout the cerebrum and in the optic nerve, but no infiltration was present in the fibers of the retina.

The authors concluded: "There are therefore no essential differences, either clinical or anatomic, between acute multiple sclerosis and neuromyelitis optica. Other acute and subacute leuko-encephalitides perhaps do not deserve to be considered as morbid entities."

A CASE OF TUBEROUS SCLEROSIS WITH PARAVENTRICULAR SPONGIOBLASTOMA. J. LHERMITTE, HEUYER and MME. CLAIRE VOGT.

A girl, aged 4 years, was brought to the hospital in a state of coma. The clinical picture was that of tuberculous meningitis; there was a history of idiocy and epilepsy, and adenoma sebaceum was present on the face. There were hydrocephalus and choking of the disks, and a roentgenogram revealed an area of calcification in the paraventricular region. Necropsy revealed tuberculous meningitis as well as changes typical of tuberous sclerosis and, springing from the wall of the ventricle, a tumor the size of a cherry made up mostly of two kinds of cells.

INTERMITTENT POLIOENCEPHALOMYELITIS OR MYASTHENIA (RECURRENT PARALYTIC EPISODES DURING TWENTY-SEVEN YEARS WITH THE APPEARANCE OF A MYASTHENIC SYNDROME). T. ALAJOUANINE, R. THUREL and R. ANDRÉ.

A man, aged 56, had the first attack of ptosis of the left upper eyelid, without diplopia or other visual disorders, in 1908. In 1916, two weeks after a small foreign body had been removed from the cornea of the left eye, ptosis accompanied by diplopia occurred, and about fifteen days later weakness of the arms was noted. The ptosis and diplopia subsided after a month; the weakness, however, lasted for three years and was especially evident in the extensor muscles of the fingers.

After receiving antisyphilitic treatment the patient was able to resume work as a metallurgist. Weakness of the arms recurred in 1926 and lasted about a month. In December 1934 the left eyelid drooped, and diplopia occurred; then ptosis developed on the right side, and in January 1935 progressive weakness of the arms appeared. Later the paresis became generalized. Fatigability of the weak muscles became more pronounced. On June 15 electrical examination showed a pronounced myasthenic reaction.

The authors hesitated to make a definite diagnosis in this case.

DISCUSSION

HENRI CLAUDE: The long period of freedom from attacks gives rise to a problem as to the evolution of myasthenia. Forty years ago a patient with typical myasthenia was hospitalized at the Salpêtrière for a long time. Ocular disorders, difficulties in speech and swallowing and ready exhaustion were present. Complete recovery occurred. During the war I saw another patient with the symptoms typical of that disease. He recovered after receiving endocrine therapy; I see him every once in a while; he is completely well. In myasthenic states there are many functional troubles resulting from toxic or endocrine disturbances; these troubles appear to be progressively disabling and yet may disappear entirely.

BILATERAL SYMMETRICAL CEREBRAL SOFTENING FOLLOWING LIGATION OF ONE JUGULAR VEIN. PIERRE DUVAL, J. LHERMITTE and VERMES.

In a man, aged 57, the jugular vein was tied when glands in the neck were resected on account of epithelioma of the tongue. Immediately after the vein was tied the respiration became stertorous. The patient did not recover from the coma that ensued, though he lived about thirty-six hours. Necropsy revealed marked congestion of both hemispheres of the brain, and in both frontal lobes there were hemorrhagic areas, which microscopically were mostly perivenous and accompanied by softening.

The authors stated that, according to Rohrbach, in a series of 91 cases of unilateral ligature of the jugular vein there were 14 deaths, of which only 1 was attributed to disturbances in the cerebral circulation. Some anomaly in the venous system, as a result of which the supply of blood on the uninvolved side is inadequate, may produce extreme venous stasis. The authors, however, expressed the belief that the occurrence of such an anomaly is rare. They thought that the stasis may be explained on the basis of the influence of the anesthetic—though, according to them, this explanation did not hold good in their case—or of interference with the sympathetic nervous system.

DIABETES INSIPIDUS APPARENTLY FOLLOWING SPRAINING OF THE ANKLE. DISTANT AND IMMEDIATE FACTORS IN POLYURIA. J. LHERMITTE, METENIER and GAUTHIER.

A healthy youth, aged 17, sprained his ankle. Within two or three days after hospitalization the daily urinary output rose from 1 to about 4 liters. It was temporarily diminished by lumbar puncture but thereafter was unaffected. Neurologic examination revealed exaggeration of the tendon reflexes on the left side; plantar excitation produced extension of the great toe of the left foot. The cremasteric reflex was lost; the abdominal reflexes were present. The patient presented a problem in the ward on account of his hostile, aggressive attitude. Roentgenograms of the skull showed considerable reduction of the sphenoid sinus and thickening of the floor of the sella turcica. In spite of the negative Wassermann reaction, it was believed that the patient was syphilitic and that the minor trauma was the immediate cause of the development of symptoms.

THICKENING OF THE BASE OF THE SELLA AND ITS SIGNIFICANCE. J. LHERMITTE and NEMOURS-AUGUSTE.

In a roentgenogram of the skull taken in the lateral position one observes occasionally a peculiarity of the sella and sphenoid in which the sphenoid sinus is much diminished and there is considerable thickening of the floor of the sella and of the quadrilateral plate, which is prolonged in certain cases to the ends of the clinoid process. The authors discovered a series of cases of this anomaly and found that the condition correlated rather highly with pituitary dystrophies and other stigmas of degeneracy. The authors suggested the name *pachybasic sellaire* for the condition.

HISTOPATHOLOGIC STUDY OF NARCOLEPSY AND OF TREMOR WITH MUSCULAR RIGIDITY. TUBERCLE OF THE FRONTAL LOBE WITH JUXTAVENTRICULAR DIENCEPHALIC LESIONS AND LESIONS OF THE STRIATE BODY. MARCEL MONNIER.

A man, aged 63, became ill six months before death with attacks of sleep, sometimes accompanied by headache and vertigo. There was some disturbance in speech and memory. Neurologically, there were a slight tremor of the left hand, associated with mild hypertonia, and some tendency toward catatonia, especially marked in the forearm. The arm reflexes were increased on the left, and the left hand was somewhat less sensitive to touch and pinprick than the right, but sense of position and temperature seemed to be normal. The spinal fluid was clear, and the pressure was not increased. The eyegrounds were normal. During the last month or two of the illness the weakness on the left side became much more marked, especially in the face, and the patient remained in coma until he died. Necropsy revealed a moderately large tubercle in the tip of the right frontal pole, with marked swelling on that side of the brain and compression of the ventricles. In addition, there were demyelinization and status cribralus in the basal ganglia and a low grade nonsuppurative ependymitis affecting the head of the caudate nucleus, the diencephalic region and the aqueduct of Sylvius. No special nucleus of the hypothalamus seemed to be involved, but the intensity of the process seemed to rule out involvement of the frontal lobe as a source of the narcoleptic disturbances. Whether the tuberculous infection excited the ependymitis as well as the formation of the tubercle was not determined. The tremor was probably caused by lesions of the extrapyramidal system.

DISCORDANCE BETWEEN THE RESULTS OF THE TEST WITH IODIZED POPPY-SEED OIL 40 PER CENT AND THOSE OF THE QUECKENSTEDT TEST IN A CASE OF TUMOR OF THE SPINAL CORD. F. COSTE and J. HAGUENAU.

A woman, aged 78, was considered by relatives to be neurotic; she complained of pains in the lower part of the back and along the distribution of the right sciatic nerve for several months before examination. There were rather typical signs of irritation of the roots of the sciatic nerve, with diminution of reflexes; the Babinski sign was not present, and there were no superficial vasomotor or trophic disturbances. Spinal puncture yielded a yellowish fluid with a high albumin content. The Queckenstedt test was negative. A cisternal injection of iodized poppy-seed oil 40 per cent showed blocking opposite the second lumbar vertebra, and an injection at a lower level outlined the tumor exactly. The tumor was removed by operation, and the patient recovered.

The authors emphasized the fact that occasionally the results of the Queckenstedt do not agree with those of tests with iodized poppy-seed oil.

VENTRICULOGRAPHY IN CASES OF BLOCK OF THE FORAMEN OF MONRO. LÉON ECTORS.

A tumor located in such a situation that it can block the foramen of Monro may cause a variety of disturbances in the ventricles. Sometimes the homolateral and sometimes the contralateral ventricle is dilated. There may be a shift to one

side or the other, and this may be participated in by the third ventricle. Occasionally by compressing both foramina the tumor may give the appearance of being a tumor of the third ventricle. In addition to a tumor, there is sometimes occlusion of the foramen of Monro by a chronic type of productive inflammation.

AMYOTROPHIC LATERAL SCLEROSIS OF POLIOMYELITIC TYPE WITH BULBAR ONSET. LÉON ECTORS.

A woman, aged 40, presented herself at the neurologic clinic on Nov. 28, 1932, complaining of disturbances in speech, slight weakness in the right arm and difficulty in swallowing. Later atrophy and fibrillation in the biceps muscle and abolition of the tendon reflexes occurred. The patient died on March 10, 1933.

Pathologic examination revealed wasting of the anterior horn, beginning at the level of the bulbar nucleus and extending to the lumbar portion of the spinal cord. There was no demyelinization, but a marked reaction consisting mainly of histiocytes and lymphocytes was evident around the vessels. Globules of fat were present in the dorsal portion of the lateral and in the anterior column.

The authors stated that the extensive perivascular reaction could be regarded as indicative of an infectious basis.

THE PERIVENTRICULAR OR SUBEPENDYMAL VEGETATIVE SYSTEM. G. ROUSSY and MOSINGER.

From this study, which is a continuation of careful investigation of this part of the brain by the authors, Roussy and Mosinger concluded that the periventricular neurovegetative system runs continuously from the lateral ventricle and the preoptic region to the spinal cord. Owing to innumerable association fibers it can be considered a functional unit, integrating the function of the whole neurovegetative system. This system presents a certain number of nuclei of condensation, more or less differentiated, such as the periangular nucleus of the lateral ventricle, the nucleus of the infundibulum (which plays a part in the innervation of the hypophysis) and the sympathetic nucleus of the third nerve. There are intimate connections between the periependymal neurovegetative system and the reticular system. The subependymal vegetative system appears to be supplied with an ependymal network of probable sensory significance, which is believed to perceive physicochemical changes and modifications in pressure of the cerebrospinal fluid. These variations may thus be relayed to the organs innervated by the periependymal system, such as the hypophysis.

CLINICAL STUDY OF A FORM OF BENIGN MYELITIS WITH PREDOMINANT SENSORY SYMPTOMS. OTTO SITTIG, Prague, Czecho-Slovakia.

Five cases were reported from the private practice of Dr. Sittig. Dysesthesias were the most prominent features. They began in the feet, rose to the abdomen and chest and were associated with insensibility and the feeling that something was interposed between the skin and the object touching it. The patients were no longer ticklish; they experienced disturbances in the sexual, rectal and vesical functions. The sensibility to vibration was particularly affected; the sense of pain and the tactile threshold were also affected. In cases in which the limbs were involved there were clumsiness and some ataxia. In some cases the Romberg sign was positive. The reflexes were increased; the Babinski sign was present in 4 of the 5 cases. The course in all cases was benign, some patients scarcely interrupting their work.

The author expressed the belief that there are three etiologic possibilities: epidemic encephalomyelitis, disseminated sclerosis and a disease sui generis of unknown etiology. In only 1 case did the relationship to disseminated sclerosis appear close, in that there was a history of preceding retrobulbar neuritis with central scotoma.

HYPOPARATHYROID COMA (DISAPPEARANCE OF THE CHVOSTEK AND TROUSSEAU SIGNS DURING THE COMA). J.-C. MUSSIO FOURNIER, P. ENGEL, J.-J. LUSSICH SIRI and J. T. FISCHER.

A woman, aged 49, underwent thyroidectomy in 1929; this was followed by tetany. Later a hypoparathyroid state with occasional generalized convulsions developed. The patient reacted well to administration of parathyroid extract. In 1935 she suffered status epilepticus with succeeding coma. Rigidity of the neck was present, but the Kernig sign was not elicited. The calcium content of the blood was 6.5 mg. per hundred cubic centimeters, and the phosphorus content, 8.25 mg. Eighty units of parathyroid extract and 8 Gm. of calcium chloride were administered intravenously, but the patient died. During the period of coma the Trousseau and Chvostek signs were no longer present.

The authors pointed out the necessity of ascertaining the phosphorus and calcium content of the blood in some cases of coma, as the ordinary signs of tetany may be absent.

TWO CASES OF INTRAMUSCULAR HEMORRHAGE DURING ALCOHOLIC INTOXICATION FOLLOWED BY CAUSALGIA. TREATMENT WITH SODIUM HYPOSULFITE. M. SMIRNOW.

The first case occurred in a man aged 35, who had slept outdoors one night in an alcoholic stupor with his legs exposed. Massive hemorrhage associated with severe pain developed in the legs. The pain subsided on the fourth day. About three weeks later, however, causalgia developed in the legs; it was associated with intense vasomotor and trophic disturbances which lasted for a number of months. Some improvement resulted from intravenous injection of a 20 per cent solution of sodium hyposulfite, but more relief was obtained by injection of 180 cc. of a 0.25 per cent solution of procaine hydrochloride into the perirenal region. Three days after receiving the injection of procaine hydrochloride the patient was able to take a few steps.

In the second case the condition was much less severe, but in this, as in the first case, the disorder developed after the patient had slept in an alcoholic stupor with his legs exposed Hemorrhages, accompanied by the usual rather pronounced reaction, occurred in both legs, and causalgia appeared in the left hand about two weeks after the onset. Daily injections of sodium hyposulfite were given and ultraviolet radiation was administered from the onset.

The authors stated that they had frequently seen subcutaneous hemorrhages in persons who had carbon monoxide poisoning but that the occurrence of such hemorrhages in persons with alcoholism is apparently much less frequent. They expressed the belief that the cause of the hemorrhage is some serious colloidal disequilibrium which sodium hyposulfite seems to overcome.

MEDULLARY COMPRESSION BY CHRONIC STAPHYLOCOCCIC EPIDURAL ABSCESS IN A DIABETIC PATIENT. RAYMOND GARCIN, PETIT-DUTAILLIS and IVAN BERTRAND.

The patient was seen about six years after the onset of paraplegia of spasmodic type. The spinal fluid was normal, and the test with iodized poppy-seed oil 40 per cent showed only a slight arrest here and there, indicative probably of myelitis associated with arachnoiditis. There was some dissociation between the albumin content and the number of cells in the spinal fluid, indicative of compression. Moreover, the roentgen examination of the spine gave negative results. The patient had had osteomyelitis of the humerus two years before the onset of the paraplegia. In spite of the presence of diabetes and obesity an exploratory operation was performed to ascertain whether there was an epidural abscess compressing the cord. Extensive epidural thickening was found, in the meshes of which some staphylococci were present. The patient died a few days after the operation.

TONIC PUPILLARY REACTION IN CONVERGENCE AND IMMOBILITY TO LIGHT IN THE PRESENCE OF UNILATERAL PARALYSIS OF THE OCULOMOTOR NERVE ASSOCIATED WITH BILATERAL INVOLVEMENT OF THE TRIGEMINAL NERVE. MARKEDLY ECCENTRIC PUPILS, OF VARIABLE LOCATION. RAYMOND GARCIN and MARCEL KIPFER.

The "tonic pupil" has been described and differentiated from the Argyll Robertson pupil, but it occurs sufficiently often in combination with loss of reflexes in the legs to mislead the unwary.

A man, aged 33, complained of bilateral facial neuralgia and showed signs of partial paralysis of the oculomotor nerve on the right side, associated with ptosis, diplopia and marked mydriasis. He had had suppurative otitis media for twenty years. There were marked atrophy of the masseter muscles and hypesthesia of the face. The right pupil did not react to light; it reacted slowly and completely in convergence. Following the effort of convergence the left pupil returned to normal size, but the right pupil required from five to ten minutes to regain its normal size. The size of the pupil, moreover, varied on different days and at different times on the same day. The pupil was markedly eccentric and at different times would be found in different locations with regard to the iris.

The authors expressed the belief that the condition was due to involvement of the long ciliary nerve occasioned by a neoplasm at the base of the skull.

HEMIALGESIC SYNDROME DUE TO PARIETAL SOFTENING. J. LHERMITTE and AJURIAGUERRA.

While severe pains and dysesthesias are known to occur chiefly in cases in which the thalamus is affected, certain disturbances are also found in cases of lesions involving other parts of the sensory tract, even as far away as the cortex.

A man, aged 57, had had a mild stroke six years before hospitalization, with a mild degree of hemiparesis and pronounced sensory disturbances, both subjective and objective. The patient always wore gloves; cold and scratching were intensely disagreeable; the fingers were rigid in extension. There was some ataxia, and astereognosis was marked. Examination of the brain showed an area of parietal softening and a narrow fissure in the right external capsule.

The authors concluded that each case must be judged on its merits and that spontaneous pains and dysesthesias are not always a sign of involvement of the thalamus.

Book Reviews

Protection of Motherhood and Childhood in the Soviet Union. Dr. Esther Conus, Chief Physician of the dispensary of the State Research Institute for the Protection of Motherhood and Infancy, People's Commissariat of Health of the R. S. F. S. R. Translated by Vera Fediaevsky. Paper. Price, 35 cents. Pp. 117, with illustrations. Moscow and Leningrad: State Medical Editorship, 1933.

The position of women in prerevolutionary Russia was a depressed and servile one, but now women have been emancipated and have complete legal equality with men. Marriage is simple, but the couple must be informed about each other's health and about any previous marriage or children. Divorce is granted at the request of either the husband or the wife. Soviet law imposes an obligation on parents for the support and care of children, whether born in or out of wedlock.

The large scale employment of women in industry has been accompanied by the making of special provisions for the protection of mothers and infants. Women are released from all work with full pay for from six to eight weeks before and for a similar period after confinement, depending on whether the employment demands physical or mental work. The nursing mother is entitled to a half-hour in every four hours to nurse her infant, and there is no deduction from her pay. A system of obstetric hospitals, supplemented by obstetric centers and traveling midwives, is a part of the program of state medicine. Free legal abortion is a state policy formulated to combat the excessive mortality which resulted from illegal abortion. Moscow railway stations are equipped to provide special food for children. Special cars for women with children have been introduced which provide shower baths, basins for washing "swaddling clothes" and a refrigerator for milk and other food.

Abortion is legally permitted during the first three months of pregnancy and is performed without charge, although an effort is often made, with varying success, to dissuade a woman from having an abortion performed when there appears to be no necessity for one. A maternal mortality rate of 1 in 2,000 abortions is reported. There remains a high annual birth rate of 40 per thousand population.

There has been an extremely rapid growth of crèches, both in cities and on state and collective farms. In 1929 there were 56,921 cots available in crèches and in 1932 there were 365,010. These crèches provide care for children under 4 years of age. These institutions are under the direction of the commissariat of health and are planned "to liberate woman from the care of her child while she is working or studying," and "to bring up a 'healthy and strong generation with nerves of steel and iron muscles' (Lenin)." The training program apparently bears a close resemblance to nursery school programs in the United States. The crèches operate also as centers for parental education.

Consultation or medical clinics for children have likewise sprung up rapidly and are supplemented by a broad health and recreation program. Preschool institutions for children from 4 to 7 years of age show a similar growth (from 308,000 children in 1928 to about 6,000,000 in 1933). Unlike crèches, they are under the control of the commissariat of education. They include kindergartens with and without boarding sections, children's rooms attached to clubs or to schools for adults (for mothers who are studying), playgrounds and orphan homes. They are administratively under the commissariat of health. The work of physicians connected with these institutions embraces sanitary and hygienic supervision, medical examinations and supervision of physical culture, as well as some work of social or organizational character in integrating these institutions with the soviet social structure.

School education is free and compulsory and seeks a simultaneous and harmonious development of mental education, physical training and polytechnic instruction. The growth of schools has not been so phenomenal as the growth of the other institutions which have been described, since many schools were established in presoviet Russia. Nevertheless, the number of pupils in primary and secondary schools increased from 7,000,000 in 1914-1915 to nearly 21,000,000 in 1931-1932.

Vocational consultation is available in the secondary schools, and medical, "psychotechnical" and "social" examinations are used in the selection of entrants for admission to factory workshops and schools. The school physicians play the principal rôle in these selections and in vocational guidance. There is an extensive development of summer camps for children of school age.

Parallel with these developments in the field of socialist construction, the Soviet Union fosters research. Obviously the present stress is on the applied sciences.

The American reader of this work is continually astounded at the rate of multiplication of soviet health and educational institutions but is often inclined to wonder at the quality attained with such mass production methods. The spectacle of a nation lifting itself by its bootstraps is none the less impressive. The English of the text is often quaint and includes obsolete phraseology, but this interferes neither with the comprehensibility of the work nor with its interest.

The Individual Criminal: Studies in the Psychogenetics of Crime. By Ben Karpman, M.D. Price, $4.50. Pp. 317. Washington, D. C.: Nervous and Mental Disease Publishing Company, 1935.

This book is a sequel to "Case Studies in the Psychopathology of Crime" and represents a sincere attempt to formulate criminal behavior in terms of processes and forces outside the subject's control. The book reveals that the offender is "a victim of circumstances," to use the criminal's jargon, but it fails in the main to get very far behind the "victim's" own superficial view of what these circumstances are. In view of the subtitle, this is especially unfortunate.

The five case histories which were given in detail in the previous volume are here presented in shorter form but are expanded with "interpretational" and "diagnostic" discussions which are more elaborate than elucidative. Interpretations are interpolated in the life histories, but there are also additional subsections on the "personality make-up" which are essentially descriptive recapitulations of the life history in respect to the criminal's overt attitudes and reactions. While in each case much important pathogenic material is given, this material appears kaleidoscopically and is not integrated sufficiently to give a clear, dynamic view of the development of a criminal career. The diagnostic sections suffer from the same defect, being compounded of discussions of general psychopathologic theories, kraepelinian categorization and superficial psychoanalytic interpretations. To each case is appended a "psychobiopsy" or "personality life chart," which might have been used to trace the main life trends as they could be discerned beneath the surface phenomena but which is here given over to a chronological report of the anamnesis.

Interpolated as appendixes to cases 3, 4 and 5 is a series of discussions of "crime mechanics." In the first discussion, entitled "Crime and Crime Causation," Karpman deals with the legislative causes of crime, the social-environmental factors in crime, the effects of imprisonment on the criminal and the effects of social attitude toward the liberated criminal. Following case 4 is a discussion by an inmate of the criminal department of St. Elizabeth's Hospital which gives a comparison of the behavior of psychopathic and that of professional criminals, the preceding case being used as a text. The same inmate discusses also "class division in crimedom," and in a final section, following case 5, which is also used as a text, the confidence game is discussed.

The concluding pages of the volume present a reprint of Karpman's paper published in the *Journal of Criminal Law and Criminology* for March-April 1935, entitled "Preliminary to the Psychotherapy of Criminals," in which he reviewed

the destructive effects of the penal system and made a plea for changes in the system, without which, he stated, psychotherapy is futile.

The criminologic discussions are by far the most informative in the book and reveal a sympathetic insight into the sociologic aspects of the problem of crime. There is an exhaustive general index as well as a valuable index to criminal jargon.

Handbuch der Neurologie. Edited by O. Bumke and O. Foerster. **Volume XIII. V: Special Neurology. III: Diseases of the Spinal Cord and Brain. II: Infections and Intoxications.** Price, 197 marks. Pp. 1,116, with 212 illustrations. Berlin: Julius Springer, 1936.

This is one of the finest of the volumes yet to appear in this extensive handbook of neurology. It is also one of the largest.

The first article is on herpes zoster, by Wohlwill. It is a good presentation of the subject and has one of the best discussions of the pathologic features of herpes of which the reviewer is aware. It reviews not only herpes affecting the spinal roots but also herpes ophthalmicus, herpes oticus and symptomatic herpes. It gives a careful review of the entire problem of herpes. There is a useful review of the findings in the nervous system in patients with rabies, by Kroll. One of the best sections is that on poliomyelitis, by Pette, who presents an exhaustive monographic study on the problem of poliomyelitis from all angles. The article is beautifully illustrated with many photomicrographs of pathologic sections from experimental animals and from human beings. Pette also discusses postvaccinal encephalitis, which includes also the forms following measles, varicella and other diseases. This subject is also well treated, but Pette makes an unconvincing attempt to demonstrate that these forms of encephalitis are similar to encephalomyelitis disseminata. There is a full discussion of epidemic encephalitis, by Stern, and a rather disappointing discussion of myelitis, by Környey. The problem of myelitis is difficult at best, but Környey's article adds little of value and does nothing to clarify it. His effort to identify many forms of myelitis as acute disseminated encephalomyelitis smacks too much of the influence of Pette's ideas to the exclusion of others. Marburg contributes an excellent discussion of multiple sclerosis but evades completely the urgent problem of acute multiple sclerosis versus encephalomyelitis disseminata.

An exhaustive and useful discussion of intoxications due to organic, inorganic, plant, animal and bacterial toxins is presented by Bumke and Kropf. In these pages are many valuable facts not available elsewhere in such handy form. All sorts of intoxications are discussed, so that the article is valuable from both an encyclopedic and a practical point of view. A similar chapter on other toxins, such as alcohol, morphine, cocaine, nicotine, coffee and tea, is contributed by Bumke and Kant. There is a good chapter on the neurologic disorders in nephritis, diabetes, pregnancy and serum disease, by Moser. Funicular spinal disease is treated by Bremer. The presentation is excellent as far as it goes, but it does not discuss adequately the relation of this disorder to avitaminosis. Bodechtel discusses the neurologic disorders in diseases of the blood. The review is useful. There is also a good chapter by Schlesinger on such diseases as scurvy, ergotism, beriberi, pellagra and lathyrism.

The volume is excellent. It reaches a high standard of quality for even this pretentious work. Both individually and as a whole, it is a fine piece of work and can be recommended without qualification. The subjects are timely and the discussions exhaustive yet practical, and the various problems are well covered from all angles.